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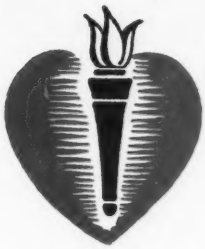

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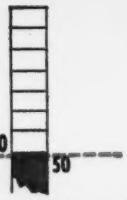
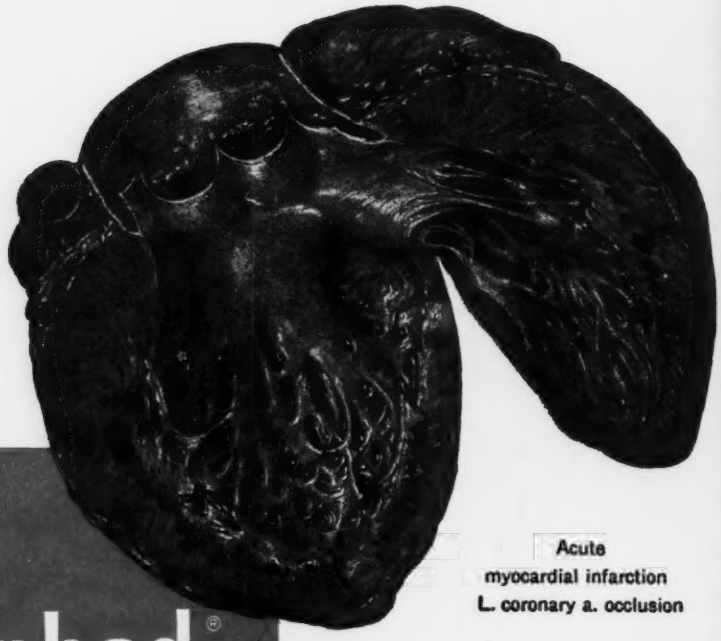


secondary to myocardial infarction



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1. Gazes, P. C., Goldberg, L. I., and Darby, T. D.: *Circulation*, 8: 883, Dec., 1953.

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Circulation
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SEPTEMBER 1954
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Studies on the Control of Hypertension by Hyphex

V. Effects on the Course of the Malignant Stage

By Henry A. Schroeder, M.D., John D. Morrow, M.D., and H. Mitchell Perry, Jr., M.D.

One hundred and six patients in malignant stages of hypertension were treated with continuous oral hexamethonium chloride and 1-hydrazinophthalazine. The courses of ten uremic individuals were unaffected. Twenty-eight discontinued therapy, three of whom survived two months. Sixty-eight nonuremic patients continued treatment and 54 are alive 15 to 36 months later; 17 who were azotemic have lived two to three years. Of the 14 who died, only three succumbed to hypertensive complications. Forty-six of the living patients have returned to full activity. Apparently the malignant stage of hypertension is reversible by drugs properly used to lower blood pressure and no longer need be the rapidly fatal disease that it has been in the past.

THE oral administration of frequent doses of hexamethonium chloride and 1-hydrazinophthalazine (Hyphex) has been shown to lower the blood pressure of all hypertensive patients as long as the drugs were given.[1-3] The use of these two agents is not "without hazard, but is justifiable when severe damage secondary to hypertension has occurred."[4] The chemical and pharmacologic reactions of the latter,[5] the therapeutic levels in blood and the excretion rates of both agents have been reported.[6] This communication is concerned with improvement in the signs, symptoms and laboratory findings associated with the malignant stages of hypertension consequent to their use, and the limitations of the method for survival in the presence of severe renal insufficiency.

Method and Material

The method of administration of these two agents has been reported previously.[7, 8] In hypertensive emergencies such as acute pulmonary edema or hypertensive encephalopathy (wet brain), the condition of the patient often precluded oral administration or necessitated rapid lowering of blood pressure, in which case drug was given parenterally until improvement occurred.[7, 8]

Control data consisted of measurements of blood pressures made by a physician prior to hospitalization, but, more especially, of levels measured by competent nurses with the patient in the supine position every four hours in hospital. The averages were compared with levels obtained by patients in the sitting position at home or at work under conditions of full activity. By this means it was believed that psychogenic influences causing abnormally elevated levels obtained by physicians during the control period might be, in the main, avoided. The postural fall of blood pressure in the sitting position induced by hexamethonium ion is seldom marked and disappears in time.

The ocular fundi were photographed in color in 35 cases and rephotographed three weeks and several months after Hyphex was begun. Renal function was measured by the level of nonprotein nitrogen in the blood (Somogi-zinc precipitation, upper limit of normal 25 mg. per 100 cc.) and by the fractional urinary excretion of phenol red (PSP), at 15, 30 and 60 minutes after intravenous injection. Alterations in cardiac status were estimated by symptoms, signs, electrocardiograms and x-ray photographs of the chest. The lability of the blood pressure during sleep induced by sodium Amytal was determined in each case. Repeated urinalyses were made, both during the initial hospital admis-

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sion, before and after the drugs were given, and on subsequent examinations.

The clinical material comprised 106 patients in malignant stages of hypertension, of whom 10 exhibited symptoms and findings of uremia, encountered in Barnes Hospital during two years. Hyphex was first used in the beginning of August 1951, in five patients. Seventy-four in malignant stages were treated during the first 13 months and the remainder during the first 21 months. For purposes of evaluation no living patient whose treatment began after May 1, 1953, was considered in this series although patients subsequently treated and dying are included. All deaths up to August 15, 1954, are tabulated.

The malignant stage of hypertension, a clinical diagnosis, was characterized by a high, "fixed" diastolic pressure, diminution of renal function, proteinuria, hypertensive retinitis with papilledema and other signs of rapid deterioration. Clinical malignant hypertension as used in this study is not to be confused with the pathologic diagnosis of "malignant nephrosclerosis" with necrosis of arterioles found terminally in patients dying with severe hypertension and azotemia.

When renal insufficiency not considered to be secondary to congestive heart failure had occurred and remained after heart failure was treated, we have classified the condition as stage IVc.[3] When renal function was diminished but adequate for normal nitrogen balance, we have classified the condition as stage IVb.

In addition, for prognostic and therapeutic purposes, we have presumed to include a group designated as the "early malignant" stage (IVa) in which two of the three findings of hypertensive retinitis (papilledema, hemorrhages and exudates) were found; high "fixed" diastolic pressure, diminution of renal function and proteinuria were essential. Papilledema was present in 10 patients, 8 showed blurring of the margins of the optic discs with hemorrhage and exudate and six showed clear discs. Justification for inclusion of this group lies in the mortality rates found by Keith and his co-workers[9] of close to 40 per cent in one year and 63 per cent in two years for patients with grade III fundi, signs of deterioration present in our cases and the frequent but not uniform progression to more serious stages; we fully realize, however, that retinitis and even papilledema may sometimes disappear spontaneously.

The malignant stage of hypertension may be superimposed upon or associated with nephrosclerosis as well as organic renal parenchymal diseases of various types. In the present series of 27 autopsied cases, pyelonephritis was discovered in two, and diabetic intercapillary glomerulosclerosis of mild degree in one, in addition to renal vascular disease. Of the remainder, pyelonephritis was suspected in five azotemic individuals on the basis of history or findings (one death) and chronic glomerulonephritis in three (two deaths); the signs of the malignant stage of hypertension were present in all cases.

There were 50 men and 56 women. Twenty-four were Negroes. Thirty-seven were ward, 69 private patients. The various subdivisions of this group are shown in table 1. All were classified by Smithwick's method,[10] which included secondary atherosclerotic complications, as group 4. According to our own classification,[3] which considers insofar as possible the hypertensive or vasospastic process only, 24 were in early malignant stages (IVa), 31 were in severe malignant stages (IVb), 41 exhibited renal insufficiency (IVc), and 10 were in uremic stages. By treating the most advanced cases encountered, it was believed that the limitations of the method could be defined. No case was refused treatment because of severity of the disease, and selection was made only by the referring physician. On admission to hospital 22 exhibited congestive heart failure, 14 cerebral edema, and nine had suffered strokes of apoplexy. Treatment of all patients was directly supervised by one of us.

Results

Gross Mortality. Of the 106 patients in whom Hyphex was initiated, 28 have failed to continue the use of one or both drugs for various reasons. Twenty-five have ceased to use both agents and three to use hexamethonium chloride (table 1). Of the 28, 25 have died (gross mortality 89 per cent); all died of the complications of hypertension. Of the 68 whose disease had not progressed to the point of uremia, 14 have died while taking Hyphex under direction (gross mortality 21 per cent). In 11, death was due to causes other than direct hypertensive complications (16 per cent). The various causes of death are shown in table 2. Papilledema was not present in the three living patients who discontinued therapy.

Mortality in Uremia. In 10 instances uremia secondary to nephrosclerosis was uninfluenced, all patients dying during the initial hospital admission. Severely elevated blood pressure, however, responded to the drugs, and hypertensive complications (left ventricular failure, convulsions due to encephalopathy) appeared to be relieved. No improvement in renal function was observed; when blood pressure was lowered only moderately the nonprotein nitrogen in the blood did not rise rapidly but did so when blood pressure was sharply reduced to normotensive levels.

TABLE 1.—*Present Status of 106 Patients in Malignant Stages Followed 15 to 36 Months*

Stage of Hypertensive Disease	Adequately Treated				Discontinuing Treatment*			
	No. Cases	Living	Dead	Mortality %	No. Cases	Living	Dead	Mortality %
Uremia	10		10	*100*				
IVc Nitrogen retention								
NPN > 60 mg. %	2	1	1	(*50*)	4		4	*100*
NPN 30–60 mg. %	25	19	6	*24*	10		10	*100*
IVb Adequate renal function	23	18	5	*27*	8		8	*100*
IVa Early malignant stage	18	16	2	*13*	6	3	3	(*50*)
Total excluding uremia	68	54	14	*21*	28	3	25	*89*

* Hexamethonium chloride discontinued in 3, both agents in 25.

NOTE: Thirty living patients have been on Hyphex for 30 to 36 months, 15 for 24 to 30 months, 6 for 18 to 24 months and 3 for 15 to 18 months. Of the 20 in Stage IVc, 11 have been treated for 30 to 36 months, 6 for 24 to 30 months, and 2 for 18 to 24 months. Of the deceased treated patients without uremia, 4 lived 12 to 15 months, 7 lived 2 to 5 months and 3 lived 1 month or less after discharge from hospital. Of the 28 discontinuing treatment, 7 were treated for 1 month or less, 7 up to 3 months, 6 up to 6 months, 4 up to 12 months and 4 for 12 to 24 months. Twenty-two of the 25 deceased patients in this group died within 2 to 30 days after discontinuing therapy and 3 within 60 days.

TABLE 2.—*Cause of Death of 39 Patients in Malignant Stages**

	Continuing Treatment (76 cases)				Discontinuing Treatment (27 cases)			
	IVc	IVb	IVa	Total	IVc	IVb	IVa	Total
Hypertensive complications								
Uremia					4 (2)†			4
Uremia developing	2			2	3	4		7
Cardiac failure					1	1		2
Cerebral hemorrhage					1	1	1	3
Cerebral arterial thrombosis		1		1			1†	1
Cerebral edema					1			1
Coronary occlusion					1			1
Sudden death while hypertensive					1			1
Unknown while hypertensive					2	2	1	5
Subtotal	2	1	0	3	14	8	3	25
Nonhypertensive Causes								
Acute interstitial pneumonia‡	2	1	1	4				
Bronchopneumonia	1	1		2				
Postoperative shock		1		1				
Carcinoma of lung			1	1				
Died in sleep—unknown while normotensive	2	1		3				
Subtotal	5	4	2	11				
Total	7	5	2	14	14	8	3	25

* Excluding 10 uremic deaths.

‡ Attributable to drugs.

† Discontinued hexamethonium chloride only.

Mortality in Renal Insufficiency. Of the 41 patients with elevated nonprotein nitrogen in the blood (stage IVc), 12 discontinued both drugs and died shortly thereafter of uremia (five cases), apoplexy (one case), cerebral edema (one case), cardiac failure (one case), coronary occlusion (one case), and of sudden and unknown cause (three cases). In two hexamethonium chloride was discontinued after 8 and 12 months while the disease appeared to be static; within a month their condition rapidly degenerated to uremia (table 2).

Among the 27 patients who continued with adequate therapy there were two instances in which nitrogen retention remained uninfluenced and static when blood pressure was moderately controlled. Signs of the malignant stage regressed, and patients were able to return to limited activity, but uremia eventually supervened three and eight months later. In these, glomerulonephritis was believed to be an associated renal lesion. The remaining five died of conditions unrelated to elevated blood pressure within 1, 1, 2, 4 and 15 months, respectively (table 2). While the gross mortality of adequately treated azotemic patients was 26 per cent, that due to the effects of hypertension (uremia) was only 7 per cent in 18 to 36 months. Seventeen have lived more than 24 months.

Mortality in Severe Malignant Stage. Of the 31 patients classified as stage IVb, eight discontinued treatment and died soon after of uremia (four cases), apoplexy (one case) cardiac failure (one case) and unknown causes (two cases). Five of 23 on Hyphex have died, but only one of hypertensive complications (cerebral arterial thrombosis), a gross mortality rate in this group of 22 per cent and of only 4 per cent from the primary disease in 15 to 36 months.

Mortality in Early Malignant Stage. Of the 24 patients classified as stage IVa, six have discontinued treatment; three of these are dead of hypertensive complications and three are living. Two of the 18 continuing treatment have died, one of pneumonia and one of carcinoma of the lung. There has therefore been a gross mortality of 11 per cent when hypertension was adequately treated but none from hypertensive causes during 18 to 34 months.

Most of the patients dying of conditions unrelated to elevated blood pressure had achieved a good therapeutic result for a period of time varying between 1 and 18 months. Exceptions were three of the four dying of acute interstitial fibrosis of the lungs, in whom control was only fair. It was improbable that the other fatal diseases affected their blood pressure levels, although the serious vascular damage already present may have made them more susceptible to intercurrent conditions. For example, two developed acute bronchopneumonia and died after two and four months of relative normotension; in one a small bronchogenic carcinoma invaded a pulmonary artery with resultant hemorrhage after 18 months of normotension; one died of shock in hyponatremia after surgical sympathectomy, performed because of two failures to cooperate in taking drugs and two consequent attacks of acute hypertensive encephalopathy; three died quietly during sleep while normotensive, possibly from cardiac causes, two a month after control was initiated and one 15 months later.

Controls. While paired cases, treated and untreated, were not followed, the mortality rates have been well ascertained in other series.[9, 10] The 22 individuals, however, who were considered to exhibit unequivocal malignant stages (stages IVb and IVc) requiring treatment and had their blood pressures controlled at normal or reasonable levels for periods of time varying from weeks to several months before stopping therapy, serve as controls in that circumstances out of our hands directed their courses. For one reason or another one or both drugs were discontinued by another physician (five cases), by the patient (14 cases), or by one of us at the request of the patient because of minor or disturbing side effects of hexamethonium chloride (three cases). All of these patients died of the effects of hypertension within 2 to 60 days. Of the group exhibiting early stages (stage IVa), six have ceased to take one or both drugs. One was unable to tolerate hexamethonium chloride by reason of an enlarged prostate; poor control of blood pressure was achieved with 1-hydrazinophthalazine alone and he died of cerebral arterial thrombosis 18 months later. Five

others discontinued both agents; two have died of the effects of hypertension. In the other three, retinitis had regressed and has not returned at the time of writing; one treated for two years has exhibited only a mild degree of hypertension during the succeeding six months.

It was necessary to discontinue 1-hydrazinophthalazine in the cases of five individuals (not included in the tables) with normal levels of blood pressure who developed late toxic reactions.[4] While the malignant stage has not reappeared, possibly because of massive doses of hexamethonium chloride, Reserpine and, in some, protoveratrine, fluctuating hypertension has returned in every case and has become severe in four.

Deaths Directly Attributable to the Drugs. Four deaths were caused directly by acute interstitial fibrosis of the lungs; in another uremic individual this lesion was discovered.[4, 7, 8] Hexamethonium ion is probably the initiating agent, for the lesion has been reported when this drug is used alone.[11]

Effects in Cerebral Edema. Cerebral edema (acute hypertensive encephalopathy) is defined as a condition with papilledema, marked hypertension, elevated cerebrospinal fluid pressure, severe cerebral symptoms, such as headache, vomiting, lethargy, restlessness and sometimes coma, and is not to be confused with cerebral symptoms due to cerebrovascular accidents (hemorrhage or thrombosis).

Fourteen patients exhibited this complex on admission to hospital. Three were pregnant. The use of hexamethonium ion intravenously and intramuscularly to lower the blood pressure gradually resulted in sufficient improvement in the cerebral status so that drugs could be taken by mouth. Too rapid lowering of blood pressure in two cases apparently caused deepening of coma. All recovered. One individual suffered three attacks, each one following poor cooperation in use of the drugs; another died of a recurrence when they were discontinued.

Present Occupational Status of Living Patients. Most of the individuals in this group either had been incapacitated by their disease, had complained of visual disturbances or were urged by their referring physicians to enter the hospital because of obvious symptoms and signs suggestive of deterioration. At the time of writing, 13 of the 16 adequately treated living patients classified as stage IVa were working or had returned to full activity and the other three to part-time activity, limited by partial hemiplegia in two cases and old intraocular hemorrhage in one. Of those in stage IVb, 17 of 18 were able to enjoy full activity or work and one part time activity. Of those in stage IVc, 16 of 20 were working or fully active and four partly so. Of those who died from nonhypertensive causes while on full treatment (14 cases), two had returned to full activity, three to partial activity and nine were invalids.

Changes in Ocular Fundi. Ninety-two patients exhibited ocular fundi of grade IV (Keith-Wagener) on admission to hospital, and 14 grade III (hemorrhages and exudates without frank papilledema). Except for the 10 uremic individuals dying during the initial hospital admission, improvement was observed in all cases. The order of regression of ocular fundal changes when hypertension was controlled was as follows: absorption of hemorrhages (one to three weeks), resolution of "soft" or "cotton wool" exudates (two to five weeks), disappearance of papilledema (two to six weeks), shrinkage of "hard" exudates (one to three months), disappearance of "hard" exudates (12 to 30 months). Poor control of hypertension resulted in persistence of "hard" exudates and even in the reappearance of hemorrhages. Improvement of ocular fundi to grade II was observed in 17 cases, to grade I in 10 cases and to practically a normal appearance in 27 cases of those who are continuing treatment.[8] In four, acute detachment of the retina was absorbed. Old intraocular hemorrhage resulting in blindness was unaffected in three.

Changes in Nonprotein Nitrogen in Blood. Of the 20 living patients initially exhibiting nitrogen retention, no change (± 10 mg. per 100 cc.) occurred in 9, a rise appeared in one (20 mg. per 100 cc.) and a slow fall to normal or near normal values (30 mg. per 100 cc. or less) was noted in 11; in none of these was azotemia believed to be secondary to congestive heart failure or other "prerenal" factors. Oc-

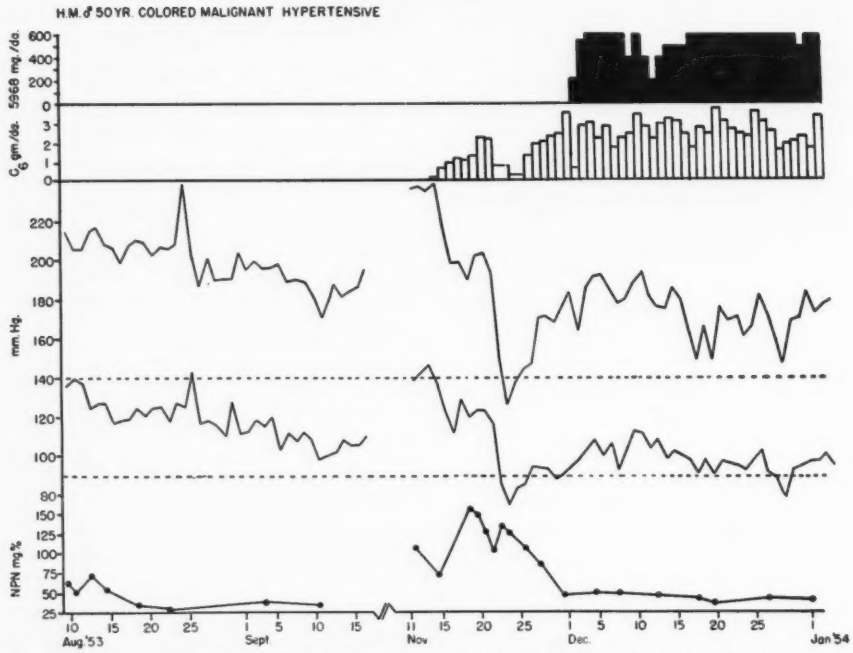

FIG. 1. Effect of Hyphex on nonprotein nitrogen in blood. H. M. was a 50 year old Negro man first admitted to Barnes Hospital in August 1953, suffering from malignant hypertension with congestive heart failure and nitrogen retention. Treated conservatively by rest, restriction of dietary salt, Rauwolfia serpentina, digitalis and diuretics, his condition improved but his underlying disease progressed. He was readmitted in November for recurrence of his symptoms. Nonprotein nitrogen in his blood had risen to 105 mg. per 100 cc. (upper limit of normal is 25 mg. per 100 cc.), congestive failure had recurred and his ocular fundi showed grade IV changes. Therapy with Hyphex was initiated. As his blood pressure fell to normal his cardiac symptoms regressed but his nonprotein nitrogen rose to 160 mg. per 100 cc. A compromise level of blood pressure was therefore chosen, high enough to allow adequate renal filtration through damaged kidneys but low enough to prevent congestive heart failure. On this regimen his nitrogen retention diminished. Lack of long follow-up excluded his case from this series. Each point on blood pressure chart represents the mean of six determinations. Patient was managed by Dr. David M. Lieberman.

casionally temporary progression was observed in hospital with the initial lowering of blood pressure, followed by a fall (fig. 1).

Regression of Proteinuria. Protein in the urine as repeatedly measured semiquantitatively by the heat-acetic acid test diminished in all cases. It disappeared in 41 cases, diminished to a trace in seven and to 1 plus in five, of which three were suspected of exhibiting glomerulonephritis. In only one did 2 plus albuminuria persist (a patient with severe renal damage in whom there had been 4 plus albuminuria).

Change in Renal Function. The renal excretion of phenol red (PSP) was measured in all cases before therapy was begun, about 20 days after, and at varying intervals later. The results are shown in table 3. General slow improvement was observed; in some cases it was striking and inexplicable. For example, in one individual the initial value was 7.5 per cent in 15 minutes; 20 days later it was 10, 5 months later it was 15, 15 months later 30, and 27 months later 37 per cent, with the total 60-minute excretion gradually rising from 45 to 75 per cent of the amount of phenol red injected.

Change in Blood Pressure. Since no single reading of blood pressure is of value as a baseline in estimating changes, the final status of the hypertension, 15 to 36 months after therapy was begun, was estimated according

TABLE 3.—*Changes in Excretion of Phenol Red (PSP)*

Stage of Hypertension	Control	2 Weeks	6 Months	12 -18 Months	No. Decreased
IVa Mean	13/55	11/46	15/51	23/62	0
Range	10–22/26–60	15–35/23–67	12–18/38–70	20–25/48–70	
S. D.	3.1/10.9	4.3/12.8	3.7/14.5	2.4/9.0	
No. Subjects	11	11	11	7	
IVb Mean	14/46	15/49	15/42	23/62	2
Range	3–30/24–70	3–27/23–74	5–30/12–93	15–30/53–75	
S. D.	12.3/12.7	10.9/19.5	15.0/20.3	3.0/8.1	
No. Subjects	13	13	10	5	
IVc Mean	3/18	5/22	7/28	8/30	0
Range	0–8/1–38	0–8/3–35	0–10/5–40	2–10/7–40	
S. D.	2.2/12.4	1.4/13.9	2.8/14.0	2.4/10.7	
No. Subjects	9	6	6	5	

The first figure is the per cent excreted in 15 minutes, the second that excreted in 60 minutes. Patients include all those with complete records. S. D. = Standard Deviation

Changes in Nonprotein Nitrogen in Blood (mg. per cent)

IVc Mean	45	41	37	33	
Range	30–90	17–90	20–95	20–89	11
No. Subjects	20	20	15	17	

Change in Average Blood Pressure (mm. Hg)

	Control	1 Year	2 Years
IVc 13 patients	223/140	169/98	
6 patients	217/136	169/100	156/94
IVb 13 patients	206/135	157/95	
4 patients	200/133	163/96	159/90
IVa 11 patients	198/123	157/92	
4 patients	206/130	160/94	148/89
Total 37 patients	209/133	161/95	
14 patients	208/133	164/97	154/91

All patients with recorded measurements made 5 times a day for a full year or two were included. The control readings were averaged from all made prior to therapy (usually six per day at four-hour intervals for a week, as recorded at rest by nurses in hospital). The same week one year and two years later, as recorded by patients on full activity, was compared (35 measurements). Note the downward trend. In the remaining 17, changes were comparable, but data were not as complete in that two to six weeks' records were unavailable.

to criteria which we have found useful.[3] The hypertension of a majority of patients was controlled at reasonable levels, as previously reported,[3] (figs. 2, 3 and 4). Improvement occurred in the long term; for example, four patients in stage IVa, four in stage IVb, and seven in stage IVc have regressed to a lesser and better therapeutic grade during the past year, while only one, deliberately reducing his dosage, has decreased his control classification. This type of gradual change has been observed since the study began.[3]

Presence or Absence of Arteriolar Necrosis. Necrosis of the renal and sometimes other arterioles usually is found at autopsy when death is the result of malignant hypertension and azotemia. It is the custom in the Department of Pathology to search carefully for this lesion. In order to ascertain whether or not this terminal change had occurred as frequently as

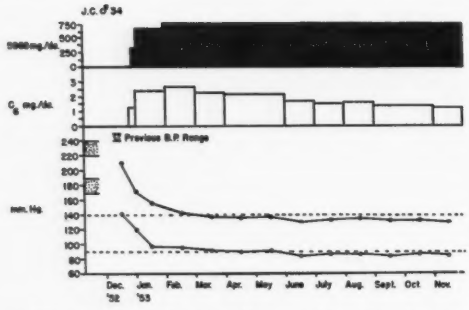

FIG. 2. Example of malignant hypertension well controlled with Hyphex. J. C. was a 34 year old man whose diastolic pressure varied between 170 and 190 mm. Hg, as recorded by his physician, for 18 months. He had suffered an attack of acute nephritis from scarlet fever at the age of 2 and his urine had persistently shown albumin and casts from the age of 17. In 1942 he was refused enlistment by the Army because of hypertension and proteinuria. Excruciating headaches had incapacitated him for several months, and visual impairment had progressed for 18 months, unaffected by full doses of veratrum viride (Veriloid). On admission in December 1952 his ocular fundi were grade IV, his heart was enlarged, proteinuria was 4 plus, excretion of phenol red was 10 per cent in 15 minutes, and nonprotein nitrogen in his blood was at the upper limits of normal. His diastolic pressure during rest varied from 130 to 170 mm. Hg. Hyphex was begun in increasing doses with excellent control of blood pressure. For three months he was mentally depressed and constipated but then began to regain his vigor. Except for the presence of 1 plus albuminuria he passed a rigid physical examination for a job in a large corporation four months after discharge from hospital, with negative cold pressor test, electrocardiogram and exercise response of blood pressure, not admitting that he was taking drugs. Two months later he passed another similar physical examination for a job in another corporation, his dilute urine showing no protein, although a trace remains in a concentrated specimen. Excretion of phenol red was unchanged after three months of treatment but after one year it was 20 per cent in 15 minutes and 45 per cent in one hour. He is asymptomatic and working full time. Each point on the blood pressure chart represents the mean of 150 determinations.

expected, autopsy reports on 22 individuals who initially showed renal insufficiency, received treatment, and died in Barnes Hospital were examined. Arteriolar nephrosclerosis characterized as "advanced" was present in every case.

In nine cases treated for one month or less

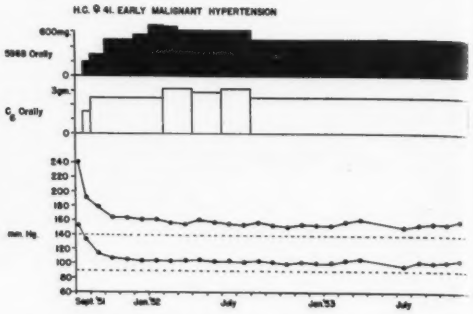

FIG. 3. Example of malignant hypertension slowly controlled by Hyphex. H. C. was a 41 year old woman suffering from severe hypertension with grade IV ocular fundi but with adequate renal function. She was partly incapacitated by severe headaches and had been unable to work in her own restaurant. Her condition was deteriorating rapidly. Her blood pressure had varied from 260/150 to 280/170 while ambulatory. A relatively poor response to Hyphex was observed in hospital even with parenteral hexamethonium bromide; resistance slowly diminished month by month until fairly good control was achieved a year later, which continued. She is working full time. Each point represents the mean of 150 determinations.

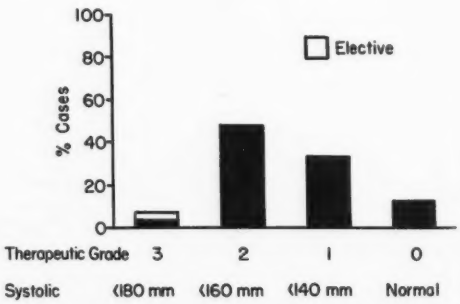

FIG. 4. Approximate degree of control of blood pressure in 54 patients previously exhibiting the malignant stages of hypertension. Each grade represents the upper limit below which four of five systolic readings lie.[3] For example, grade 3 indicates that 80 per cent of readings were below 180 mm. systolic and none was over 200; grade 1 that 80 per cent were below 140 mm. and none was over 160. The open square indicates that high levels were deliberately chosen for individuals with nitrogen retention or prior unsuccessful sympathectomy in whom lower levels would have been hazardous or uncomfortable. Data for the most recent available two weeks of therapy were so evaluated.

and dying with renal insufficiency, renal arteriolar necrosis was found in seven; the other two exhibited marked renal arterial narrowing, one showing in addition pyelonephritis and the other mild intercapillary glomerulosclerosis. In eight cases treated one to three months and dying with renal insufficiency, the lesion was found in three; one other exhibited atherosclerotic narrowing of the renal artery. In five cases treated 3 to 12 months, the lesion was found in only one, a young Negro woman who had been uncooperative in taking her drugs and died after surgical sympathectomy. Terminal levels of nonprotein nitrogen in blood varied from 45 to 260 mg. per 100 cc. in those with arteriolar necrosis (average 159 mg., four being less than 100 mg.) and from 47 to 310 mg. per 100 cc. in those without necrosis (average 151 mg., three being less than 100 mg.).

Discussion

The analysis of these data makes clear that the malignant stage of hypertension, adequately controlled by two differently acting drugs given together, may no longer be the rapidly progressive, fatal disorder that it has been in the past, provided that renal insufficiency or cerebral atherosclerosis is not advanced. Since 45 of the living patients here evaluated, 17 of them with nitrogen retention, have been on Hyphex for 24 months or more and have remained in apparent good health, the interval seems adequate for appraisal. The high death rate in the subjects discontinuing therapy indicates the necessity of continuation; the relatively high death rate from nonhypertensive causes in those on therapy stresses the severity of the generalized disease and their susceptibility to other fatal disorders, especially when cardiovascular and renal breakdown has occurred. These therapeutic agents, however, have extended the range of therapy beyond the limits previously possible with neurosurgery and other less specific methods, for the life expectancy of patients with renal insufficiency and malignant hypertension is short and subject to little extension by usual procedures.

We believe that the test of these two agents used together (Hyphex) was the most severe possible to devise. The conclusions to be drawn are: (1) that severe renal insufficiency is usually, and uremia is always irreversible; (2) that signs common to the malignant stage of hypertension can be reversed and do not recur during the period of observation if the blood pressure is controlled at "reasonable" levels; and (3) that patients with severe cardiovascular and renal disease may die of other causes when hypertension is treated. There is no evidence that the necrotizing arteriolar lesions of malignant nephrosclerosis can be reversed, but the data suggest that occasionally they may not develop when the blood pressure is lowered for several months in the presence of slowly progressive azotemia.

The study also points out the many signs of the malignant stage which are either dependent upon the elevated blood pressure or on some concomitant metabolic process affected by the drugs; retinitis, papilledema, diminished renal function, proteinuria. Furthermore, it stresses the relationship between congestive cardiac failure and left ventricular work, for no deaths have occurred from this common termination of the malignant stage, although 22 of these patients exhibited failure before treatment was begun.

This study has demonstrated that control of severe hypertension is consistent with life and normal activity for a year or more. The data suggest that the underlying process usually remains stationary or regresses rather than progresses. Unfortunately one of the drugs used, hexamethonium ion, carries with it the risk of death from acute interstitial fibrosis of the lungs, especially for males and Negroes with partly controlled hypertension.[4] Because the other, 1-hydrazinophthalazine, carries with it the risk of collagen disease,[4, 12, 13] all patients cannot be expected to control their blood pressures at unhazardous levels indefinitely unless alternative agents are developed. Discontinuation of either one of the two drugs reimposes upon the organism the strain of recurring hypertension and its consequences. Therefore, the results here reported represent merely a first approximation of specific therapy obtained only in cooperative

patients with drugs that are far from ideal. Newer agents now under test make it likely that the Hyphex method is obsolescent in that hexamethonium ion, and perhaps the substituted hydrazines, may be replaced by better drugs.

Some consideration of the efficacy of this form of therapy in malignant hypertension can be made by comparing the present mortality with that in a similar series of 104 patients with papilledema treated by conventional methods reported by Schottstaedt and Sokolow.[14] Only 12 survived 18 months and 9, 30 months or more. The average duration of life was 8.7 months with two-thirds dying within 9 months; in only three instances was it believed that a remission was spontaneous. Of the survivors, six were rigorously treated by low-sodium diet or surgery. The results here reported indicate that, excluding frank uremia, significant reduction of mortality can be achieved in patients in our stages IVc and IVb, in that a gross mortality rate of 24 per cent was found in 15 to 36 months, while that due to known hypertensive complications (uremia, apoplexy, cerebral edema, cardiac failure, coronary occlusion) was 6 per cent.

Summary and Conclusions

Oral hexamethonium chloride and 1-hydrazinophthalazine were given according to established methods to 106 patients exhibiting the malignant stages of hypertension. Twenty-eight discontinued their use after variable periods of time; 25 died, all of hypertensive complications. The courses of 10 uremic individuals were unaffected. Of the 68 who continued treatment, 14 have died, 3 as a result of hypertensive complications. Controlled hypertension is, therefore, compatible with life for at least 15 to 36 months, even when the malignant stage has supervened.

Sumario Español

A 106 pacientes exhibiendo el estado maligno de hipertensión se les administró cloruro de hexamethonium y 1-hydrazinophthalazine oral de acuerdo a los métodos establecidos. Veinte y ocho descontinuaron su uso luego de intervalos variables; 25 murieron, todos con complicaciones hipertensas. El curso de 10 individuos urémicos no fué afectado. De los 68 que continuaron tratamiento, 14 han muerto, 3 como resultado de complicaciones hipertensas. Hipertensión controlada es, de manera, compatible con vida por lo menos de 15 a 36 meses, aún cuando el estado maligno este presente.

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Intravenous Trypsin

By Alexander Taylor, M.B., Ch.B. (Edin.), and Irving S. Wright, M.D.

Studies were carried out regarding the effect of intravenous trypsin on rabbits. These included investigations into the toxicity and the tendency for the production of intravascular coagulation. The effect on artificial preformed thrombi was also observed. It was found that in the doses used, the intravenous administration of trypsin was not efficacious in the treatment of intravascular thrombosis. These studies failed to provide evidence to justify its use as a therapeutic agent in man.

INTEREST in the possible therapeutic value of crystalline trypsin, administered intravenously, has been stimulated by favorable reports by Innerfield, Schwartz and Angrist.[1, 2, 3] These investigators have claimed that trypsin may be safely administered intravenously, provided the concentration and rate of administration of the solution is strictly controlled. From their animal studies with this substance they have reported lytic effects on preformed artificial thrombi and, in certain dosage, consistent "complete dissolution of the thrombus with restoration of circulatory integrity." Recently they have reported beneficial results following its administration to 538 patients,[3] but in their report an antiinflammatory effect was stressed rather than a thrombolytic one.

One of the earliest statements concerning blood coagulation and trypsin was made by Wright[4] in 1915. At that time, he said: "The antitryptic power of the blood fluids represents, be it noted, much more than merely a power of inhibiting microbic growth. With the loss of antitryptic power are lost also the complementing, opsonic, bactericidal and coagulating powers of the blood." The following year Douglas and Colebrook[5] indicated that Wright's report had influenced them in their search for an ideal blood culture medium. They reported his observations and stated: "Emery, continuing these investigations, showed that by neutralizing the antitryptic power of the serum with trypsin the bactericidal action and other bacteriotropic properties of the serum were destroyed. From the same laboratory came the fact that when sufficient trypsin was added to the blood to neutralize the antitryptic power of the blood fluids no clotting took place." Douglas and Colebrook then carried out some investigational work of their own and reported as follows: "Further experiments were carried out to find the effect of various dilutions of trypsin on the clotting time of the blood. The result obtained was that a dilution of trypsin of about 1 in 30 completely inhibited the clotting power whereas weaker dilutions had the effect of making the blood clot very much more rapidly."

This paradoxic action of trypsin has been repeatedly confirmed in later literature but has not as yet been adequately explained. It is more or less agreed that an excess of trypsin in the blood results in inhibition of coagulation because one or more of the blood clotting components is partly or completely digested. The fact, however, that in smaller amounts it accelerates coagulation has proved to be a more complex problem. Dale and Walpole,[6] in 1916, observed that a "formation of kinase and (in the presence of calcium) thrombin occurs when fowl's plasma is treated with an appropriate proportion of trypsin." In 1917, Heard[7] observed that trypsin solutions in certain concentrations will clot oxalated blood and offered the following explanation: "Trypsin being especially active in disturbing the P and Ca in the protein molecule it is held to be probable that the surface forces brought into action by the disturbance of these atoms are the principal cause of the clotting." In 1928, Waldschmidt-Leitz[8] suggested that trypsin

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accelerated coagulation by hastening the enzymatic hydrolysis of fibrinogen by thrombin. In 1935, Mellanby[9] stated his belief that the coagulation observed by Heard was simply due to traces of calcium present in the commercial trypsin preparation. In 1937, however, Eagle and Harris,[10] illustrated "the fact that coagulation is observed only within a comparatively narrow optimum zone of trypsin concentration." They pointed out that trypsin, unlike papain, does not coagulate fibrinogen which contradicted the theory of Waldschmidt-Leitz that trypsin is analogous to thrombin. On the basis of their experimental work they came to the conclusion that trypsin activated prothrombin to thrombin and that it is therefore analogous to the physiologic system, calcium plus platelets (or calcium plus tissue extracts). They further suggested tentatively that calcium plus platelets constituted a proteolytic enzyme. The role of trypsin and of tissue proteolytic enzymes (tryptase or plasmin) on blood clotting has been studied in detail by Ferguson and co-workers,[11, 12] and interesting related experiments have been conducted by Kleinfeld and Habif.[13]

Eagle and Harris[10] then injected trypsin intravenously into rabbits and reported that it caused almost immediate death, large blood clots being found in the heart and large vessels at autopsy. They concluded that "trypsin thus seems to initiate blood coagulation in vivo as readily as it does in vitro." This observation was confirmed by Tagnon[14] and others.

In view of these early reports the intravenous administration of trypsin had seemed inadvisable, but following the reports of Innerfield and co-workers, it was decided to carry out independent animal experiments in our laboratory. The results of some of our work are here described briefly and our conclusions presented. The lyophilized crystalline trypsin (Armour Enzar) used in these experiments has been stated to be composed of 90 per cent pure trypsin, 5 per cent magnesium ash, 4 per cent traces of ribonuclease plus cathepsin and alpha, beta and gamma chymotrypsin, and 1 per cent undetermined matter. Two thousand Armour units of trypsin (Enzar) correspond approximately to 1.1 mg. by weight.

Results of Animal Experiments

I. *Toxicity*

Twenty mg. of trypsin in 10 ml. of saline were administered intravenously over a period of 45 seconds to each of six 3 Kg. rabbits. All six animals died almost immediately after a few brief convulsions. Autopsy examination revealed large adherent blood clots in the chambers of the right side of the heart in every case.

It was then found that if the trypsin solution (20 mg. per 10 ml. of saline) was administered more slowly, over a period of 15 to 20 minutes, the mortality rate was reduced to approximately 50 per cent. The concentration of the solution also appeared to be a factor involved in the mortality rate, and it was soon found to be possible to administer 100 mg. of trypsin in 200 ml. of saline at an approximate rate of 15 drops per minute with the same approximate mortality. Local phlebothrombosis, cold cyanosed ears and dyspnea were frequent complications noted during administration. Soybean trypsin inhibitor administered to the animal immediately prior to the trypsin (in doses equivalent in milligrams to the trypsin dosage about to be given) eliminated the mortality rate. The use of a trypsin solution buffered to the pH of rabbit blood was no less lethal than the unbuffered solution.

II. *Results of Intravenous Administration*

It was found that the intravenous administration of small amounts of trypsin (5 to 15 mg.) had no detectable effect whatever on the blood clotting mechanism, whereas large amounts had a marked effect on the blood clotting mechanism.

III. *Results of in Vitro Studies*

A. It was confirmed that there is a narrow optimum zone in which small amounts of trypsin will accelerate blood coagulation. In large amounts blood coagulation is completely inhibited. Soybean trypsin inhibitor when added to the trypsin solution in various

TABLE 1.—*Effect of Small and Large Amounts of Intravenous Trypsin on the Blood Coagulation Mechanism*

Trypsin	Clotting Time (*min.*)	Prothrombin Time (*sec.*)	Calcium Chloride Time (*sec.*)	Antithrombin clotting Time (Quick's Method) (*sec.*)	Proconvertin Time (Owren's Method) (*sec.*)	Fibrinogen mg.%	Total Protein Gm.%
Control	4.5	8.5	45	27	58	270	5.1
15 mg.	5	8.2	48	28	58	270	5.1
120 mg.	∞	∞	∞	16	57	Absent	4.8

∞ Represents infinity.

amounts resulted in inhibition of the trypsin effect on the blood coagulation mechanism.

B. Using oxalated blood, results of a similar nature were obtained but clotting times were less rapid. The addition of calcium along with the trypsin, however, resulted in accelerated clotting times which approached those obtained with trypsin and unoxalated blood.

C. Oxalated rabbit blood was treated with barium carbonate to remove the prothrombin. It was then found that the blood could still be clotted by the addition of thrombin but not by the addition of trypsin.

D. It was confirmed that, when trypsin is brought into contact with fibrinogen or thrombin, changes result which prevent coagulation. It is believed that this inhibition of coagulation is the result of partial or complete digestion of the thrombin or fibrinogen, but this has not been finally determined.

E. Using fibrin plates prepared according to the method of Astrup and Müllertz[15] it was found that no evidence of fibrinolytic activity of rabbit plasma could be demonstrated during a trypsin infusion until approximately 100 mg. had been administered. At this stage there was free trypsin in the plasma as it could be used to clot oxalated rabbit plasma and could be inhibited by soybean antitrypsin. It was also demonstrated by the use of these plates that normal rabbit plasma has considerable antitryptic properties, as it can protect any portion of the fibrin on which it is spread from proteolysis by a trypsin solution which has dissolved the unprotected portion of the plate.

F. When a trypsin solution is added to a solution of Overman's thromboplastic inhibitor[16] in various amounts, a mixture results which causes marked acceleration of the clotting time of rabbit blood.

G. Heparinized blood can be clotted by trypsin solutions within a very narrow concentration range. This finding is contradictory to the findings of Tyson and West.[17]

IV. *Inhibition of Trypsin-Induced Intravascular Coagulation*

Experiments were then carried out to determine whether any of the anticoagulants could prevent intravascular coagulation and death by trypsin. Heparin was found to be such a substance, thus confirming the reports by Tagnon,[14] by Schultze and Schwick,[18] and by Kleinfeld and Habif.[13] The exact mechanism of its protective effect is uncertain. The last named authors feel that it acts by increasing plasma antithrombic activity. Dicumarol in doses which resulted in a prothrombin time four times greater than normal did not protect the animals but in two rabbits 150 mg. of cyclocumarol resulted in a prothrombin time greater than three minutes, a potentially dangerous level. In these two cases trypsin was administered rapidly without death occurring. A thrombin solution administered slowly until the blood was incoagulable also resulted in a considerable reduction in the death rate due to intravenous trypsin, the only deaths in this particular series being due to hemorrhages.

V. *Potentiation of Trypsin-induced Intravascular Coagulation*

In view of the fact that trypsin and thromboplastic inhibitor together form an extremely active coagulating agent in vitro it was decided to determine whether it would result in intravascular coagulation and death when

TABLE 2.—*Effect of Trypsin on Clotting Time of Rabbit Blood (in Glass Tubes) and Influence on this Clotting Time of Calcium, Thromboplastin Inhibitor, Heparin and Barium Carbonate*

	Trypsin Concentration (mg. per 0.1 ml. distilled water)						
	Control	0.01	0.1	0.2	0.5	1.0	2.0
							Secs.
Normal blood (1 ml.)	330 secs.	105 secs.	50 secs.	34 secs.	30 secs.	∞	∞
Oxalated blood (1 ml.)	∞	∞	180 secs.	60 secs.	45 secs.	∞	∞
Oxalated blood (1 ml.) plus 0.1 ml. of 0.025 M calcium chloride	∞	95 secs.	30 secs.	28 secs.	25 secs.	∞	∞
Normal blood (1 ml.) plus thromboplastin inhibitor (2 mg.)	440 secs.	10 secs.	10 secs.	<5 secs.	<5 secs.	<5 secs.	∞
Normal blood (1 ml.) plus 0.5 mg. heparin	>6 hrs.	>6 hrs.	>3 hrs. <4 hrs.	84 secs.	420 secs.	∞	∞
Oxalated blood treated with barium carbonate (1 ml.)	∞	∞	∞	∞	∞	∞	∞

administered intravenously. This was proven to be the case, a mortality rate resulting which was even higher than that due to trypsin alone. At autopsy large adherent blood clots were found in the right side of the heart, and also in the great veins and the pulmonary arteries.

VI. *Pathology*

Almost all animals dying in the early stages of a trypsin infusion exhibit large adherent blood clots in the right auricles and ventricles at autopsy. Fairly frequently clots were also found in the large veins and in the pulmonary arteries. Hemorrhages into the lungs and myocardium were occasionally noted in the early stages, but these were the commonest lesions found at autopsy when death occurred during the latter part of the infusion, particularly after 35 mg. per kilogram had been administered and the blood was incoagulable. Retroperitoneal hemorrhages were also occasionally noted at this time.

A number of animals which survived the intravenous administration of varying doses of trypsin (from 8 to 110 mg.) were sacrificed 48 hours after the infusion. Microscopic examination of the tissues of these animals by Kellner[19] revealed the presence of numerous isolated areas of necrosis in the myocardium and in the musculature of the diaphragm. These lesions were unrelated to areas of hemorrhage, or to thrombosis or emboli.

VII. *Electrocardiography*

An electrocardiographic study of animals receiving intravenous trypsin was then carried out. In a controlled study tracings taken by Lieberman and colleagues[20] showed that changes in the record frequently occurred when 20 mg. and over were administered in a fairly concentrated solution, (1 mg. trypsin per milliliter saline). These changes were not observed during similar infusions with saline nor with solutions of the same pH as the trypsin solution. Similar changes were, however, seen when a thrombin solution (1000 units per 100 ml. saline) was slowly infused. When some of the animals which exhibited electrocardiographic changes following the trypsin infusion were sacrificed and autopsied 48 hours later, small isolated areas of necrosis were noted in the myocardium and diaphragm.

VIII. *Effect on Artificial Preformed Thrombi*

An attempt was then made to determine the effect of intravenous trypsin infusions on preformed artificial thrombi. Sections of the peripheral ear veins of many rabbits were thrombosed using thrombin (200 units) or a sclerosing agent known as sodium Sotradecol (brand of sodium tetradecyl sulfate). Within

eight hours of the thrombosing process in each case, the trypsin infusion was begun and doses varied from 10 mg. on five successive days to 150 mg. on four successive days. Single doses of 100 mg. and successive doses of 50 mg. were also administered. The trypsin solution in every case contained approximately 0.55 mg. trypsin per milliliter saline. During these infusions 40 per cent of the animals died and 35 per cent developed a thrombosis of the ear vein into which the trypsin was being administered. In no single animal was any reduction noted in the size of the thrombus. The vein remained palpable and on transillumination no return of blood flow was noted. In several animals an actual extension of the thrombus was evident.

Discussion

On the basis of these animal experiments, using a wide range of dosage, it would appear that the intravenous administration of trypsin is of doubtful value in the treatment of intravascular thrombosis. We have been unable to confirm the observation that in similar experiments with rabbits "complete clot dissolution and restoration of circulatory integrity consistently occurred at a range beyond 200,000 units of trypsin." Indeed, extension of the preformed thrombi was noted in many animals.

In a recent report Innerfield and associates[3] have described the results of intravenous trypsin therapy with 538 patients. They stated that intravascular coagulation did not occur in these cases. An antiinflammatory effect, however, was emphasized rather than the thrombolytic one which they stressed in their earlier reports. The dosage of trypsin used in the latter study was markedly reduced as compared with earlier reports. Formerly 100,000 to 250,000 Armour units of trypsin diluted in 250 ml. of saline were administered once or twice a day, but recently they have recommended 50,000 to 100,000 units twice daily in 100 ml. of saline. Intramuscular administration has also been suggested, using doses as low as 20,000 units. There is, however, no conclusive evidence that trypsin thus administered has any physiologic or therapeutic effect.

Independent clinical experiments carried out by Laufman and Roach,[21] using 250,000 units dissolved in 500 ml. of isotonic saline, did not result in any evidence that intravenous trypsin therapy caused the disappearance of a palpable thrombus any more rapidly than did conventional treatment. Their animal experiments indicated that "one cannot expect to dissolve a preformed thrombus with intravenous trypsin administration almost regardless of dosage." The clinical experience of Ormond and Knight[22] has been somewhat similar and multiple thromboses at the sites of injection have been encountered by them and by others.

The process by which trypsin coagulates blood within a narrow concentration range is an interesting and as yet unexplained phenomenon. It is apparent on the basis of our work and on that of others that prothrombin must be present in the blood if trypsin is to clot it. Trypsin itself will not coagulate fibrinogen, and therefore it would appear fairly certain that trypsin results in the conversion of prothrombin to thrombin and that this latter agent then coagulates the fibrinogen. As demonstrated by Kleinfeld and Habif,[13] calcium and accessory factors are not essential to this action, but calcium will accelerate the rate of thrombin formation without affecting the thrombin yield. Conversion of prothrombin by trypsin is apparently incomplete.

The fact that trypsin will coagulate heparinized blood under certain conditions, and that it will form a product with Overman's thromboplastic inhibitor which clots blood even more rapidly than trypsin alone, lends support to Overman's theory pertaining to thromboplastic activity.[16] According to this theory an equilibrium reaction is postulated to explain thromboplastic activity. "This consists of a phosphatide fraction I and a protein fraction, α, which are in equilibrium with αI (thromboplastin). The activity of the thromboplastin or the rate of activation of prothrombin depends upon the concentration of (thromboplastin) in the system." The phosphatide in-

hibitory fraction (designated as I) is a powerful anticoagulant and can produce prolonged prothrombin and clotting times. Overman does not believe that the calcium ion is necessary for the activation of prothrombin but does believe that the concentration of αI (thromboplastin) can be controlled by varying the calcium ion concentration. Into such a theory trypsin fits remarkably well as an "alpha-like" substance.

On the basis of this theory it may be postulated that blood will clot when "alpha" (in this case trypsin) is in equilibrium with the phosphatide thromboplastic inhibitor which is normally in excess in the blood. Heparin, we believe, may combine with alpha thus releasing the lipid coagulation inhibitor I, and therefore the heparinized blood will clot when sufficient alpha-like substance, such as trypsin, is introduced into the blood to reach an equilibrium with the inhibitor. The fact that large amounts of heparin apparently prevent trypsin-induced coagulation in vivo may be explained on the supposition that so much alpha is removed by the heparin that trypsin is unable to substitute for the missing alpha before its proteolytic effect on the blood coagulation components comes into effect. The fact that trypsin and thromboplastic inhibitor in combination form an extremely active clotting agent in vitro and a potent intravascular coagulation agent is in harmony with this hypothesis.

When trypsin is successfully administered intravenously in large doses the blood becomes incoagulable, the prothrombin and calcium chloride times are prolonged indefinitely, the factor V and antithrombic levels are reduced and the fibrinogen is eliminated. This may well be the result of enzymatic proteolysis of the protein blood coagulation components. Relatively high quantities of the amino acids, arginine and lysine, are known to be present in fibrinogen, and trypsin is known to be particularly potent in breaking the amide linkages of many arginine and lysine compounds.[23] This would help to explain the apparent marked predilection of trypsin for fibrinogen.

Conclusions

On the basis of these experiments there appears to be grave doubt regarding the advisability of using trypsin intravenously for therapeutic purposes in man. Trypsin infusions in rabbits did not result in dissolution or lysis of preformed artificial thrombi but did result in a high proportion of cases, in necrotic lesions in the myocardium and diaphragm and death from intravascular thrombosis or hemorrhage. Small amounts of trypsin in vivo have little or no effect on the blood clotting mechanism, whereas larger amounts frequently result in intravascular coagulation and later incoagulability of the blood. In vitro experiments confirm the earlier observation that there is a narrow zone of trypsin concentration within which blood coagulation is accelerated, whereas in larger concentrations coagulation is inhibited. While heparin in certain concentrations may inhibit the clotting effect of trypsin, the maintenance of the exact proportions for clinical purposes has not as yet been satisfactorily worked out.

Summary

The literature concerned with trypsin and blood coagulation has been reviewed and earlier experiments confirmed. Experimental intravenous administration of trypsin to rabbits with artificial preformed thrombi failed to provide evidence to justify its use as a therapeutic agent in man.

Sumario Español

Se hicieron estudios relacionados al efecto de la tripsina intravenosa en conejos. Estos incluyeron investigaciones en cuanto a la toxicidad y la tendencia a la producción de coagulación intravascular. El efecto en trombos previamente formados artificialmente también se observó. Se encontró que en las dosis en que fué usada, la administración de tripsina intravenosa no fué eficaz en el tratamiento de la trombosis intravascular. Estos estudios no tuvieron éxito en proveer evidencia para justificar su uso como un agente terapeútico en el hombre.

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The Effect of Intravenous Trypsin Administration on the Electrocardiogram of the Rabbit

By JERROLD S. LIEBERMAN, M.D., ALEXANDER TAYLOR, M.B., CH.B. (EDIN.), AND IRVING S. WRIGHT, M.D.

The intravenous injection of trypsin into rabbits resulted in marked changes in the rhythm and alteration in the P, QRS, S-T and T deflections of the electrocardiogram.

IN the course of animal experimentation, it was noticed in our own laboratory[1] and elsewhere[2] that the intravenous administration of solutions of trypsin was frequently followed by death of the experimental animal. Autopsies revealed the presence of large adherent thrombi in the pulmonary artery and right heart of these animals. The detailed pathologic studies of Kellner and Robertson[3] point to an effect of trypsin, as well as other proteolytic enzymes, directly on the myocardial cells. In view of these findings it seemed desirable to determine whether intravenous trypsin would produce significant alterations in the electrocardiogram of a suitable experimental animal.

METHOD

Market-bought rabbits, weighing between 3 and 5 Kg., of both sexes, were maintained on a standard laboratory diet. They were anesthetized with pentobarbital, using between 0.5 and 1.0 cc. of pentobarbital sodium, 50 mg. per cubic centimeter, intravenously. The animals were fastened to a narrow animal board, with the four paws extended. The trunks were wrapped with an elastic bandage in order to minimize any change in the position of the animal which might produce changes in the form of the electrocardiogram. Electrical contact was established by passing metal pin electrodes through the soft tissues of each paw. These were then connected to the appropriate leads of a Sanborn Twin-Viso electrocardiograph, and the bipolar leads of the frontal plane were recorded at frequent intervals, at a paper speed of 50 mm. per second. All records were standardized at 1.7 cm. per millivolt.

A fresh solution of trypsin was prepared for each infusion. Enzar* was used in a concentration of 1 mg. per cubic centimeter and was infused into an ear vein of the anesthetized rabbit at a rate of 0.2 to 1.0 cc. per minute. The rate of infusion was limited by the occurrence of thrombosis at the site of injection at low rates, and sudden death with rapid rates. In many experiments, electrocardiographic observations were continued after the completion of the infusion, if the animal lived.

Thrombin was prepared in a fresh solution of 50 or 100 mg. per cubic centimeter and infused at a comparable rate.

Normal saline solutions were utilized as a control, and were infused by similar technics, at approximately the same rates of infusion. The same electrocardiographic observations were made.

RESULTS

The form of the initial electrocardiogram resembled that described by Levine.[4] The usual rate was approximately 300 per minute, with T waves upright and of significant voltage in leads II and III, generally upright but of low voltage in lead 1. There was usually rightward deviation of the electrical axis, and the T waves were generally found to be upright in all three leads, with leads II and III being greater than lead I. Deviation of the S-T segment from isoelectricity was not observed to exceed 0.1 millivolt. Except for runs of coupled rhythm, which appeared shortly after the animals were pinioned to the board, and generally disappeared within 5 or 10 minutes, no arrhythmias were observed in the resting electrocardiograms.

In six rabbits, electrocardiograms were taken before and after the usual dosage of pento-

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* The Enzar used in this study was supplied through the courtesy of Armour and Company.

barbital. Marked reduction in obviously extracardiac muscular activity and stabilization of the baseline were seen after the animals had been suitably narcotized. In no case did the anesthesia have a lethal effect, nor was the administration of this drug followed by any significant change in the form of the electrocardiogram, other than the suppression of the ectopic focus which had previously produced the coupled rhythm.

Ten animals received infusions of normal saline by the same technic and rate of administration as that used in experimental runs. In one of the animals, a slight leftward deviation of the electrical axis of the P wave was observed. Otherwise, there was no discernible effect on the rhythm, or in the form of the electrocardiogram. QRS, S-T and T waves were unchanged.

Approximately 50 rabbits received intravenous trypsin. A number of the experiments were terminated prematurely by local thrombosis or sudden death of the animal. Of 24 successful infusions into individual animals, four showed no significant alterations in the electrical activity of the heart. One showed no changes until a point so close to death that the changes were considered terminal. The remaining 19 showed significant alterations during or following the intravenous administration of this proteolytic enzyme.

Twelve of the animals showed significant alteration in their P waves. The most frequent occurrence was rightward deviation of the electrical axis of P, usually with an increase in the magnitude of the electrical vector. This can be seen in figure 1. This occurred in six animals; six more evolved various nonspecific alterations (fig. 3). These changes often continued to evolve after the infusion had been completed.

Ten rabbits evolved definite changes in the intrinsic structure of the QRS complexes in the frontal plane. In seven, these continued during the period of observation, and frequently consisted of a change in the direction and magnitude of the initial component of the complex, such as the appearance of the R_1 shown in figure 3. Three other rabbits developed marked alterations in the form of the QRS (figs. 2, 4), which did not persist throughout the period of observation, but reverted to a form generally similar to that of the control. These were presumed to represent intraventricular conduction defects and usually were followed by persistent ST-T alterations.

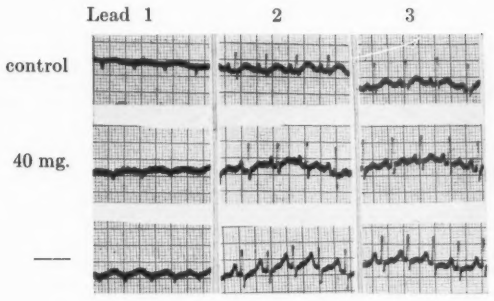

FIG. 1. After 40 mg. Enzar. Increased amplitude of P in leads II and III and definitely increased voltage of S in leads II and III is apparent. Minor alterations of S-T in leads II and III are present. Seventy-five minutes later further increase in magnitude of P_2, and definite alterations of all ST-T deflections are present, and the elision of T and P is apparent. This animal did not die.

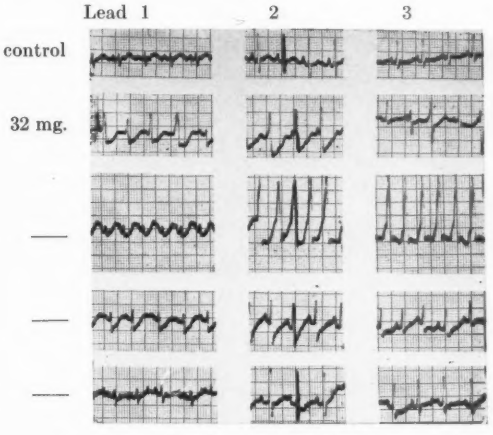

FIG. 2. Administration of Enzar, 32 mg., produced marked downward shift of the pacemaker, with intermittent conduction defects, sometimes suggesting "accelerated conduction." Marked ST-T wave alterations persist, after the restoration of normal conduction. In lead II, one complex of each strip has been overlined for reproduction. The lower strips were taken immediately, 5, 10, 50 minutes after the termination of the infusion.

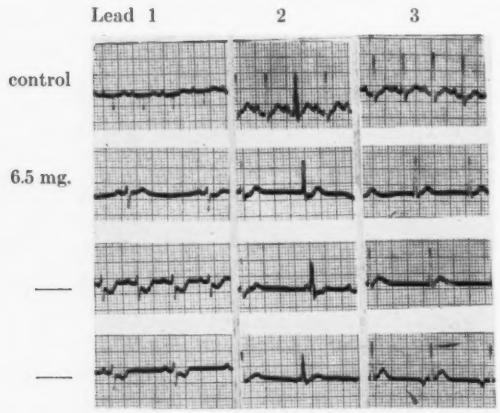

FIG. 3. Administration of 6.5 mg. of Enzar produced marked downward displacement of the pacemaker, with relative bradycardia and alteration of the intrinsic form of the QRS. The lower strips were taken 2 and 10 minutes after the infusion was terminated, at a time when reflexes and respirations were observed. Fifteen minutes after end of infusion, the animal was clinically dead. In lead II one complex of each strip has been overlined for reproduction.

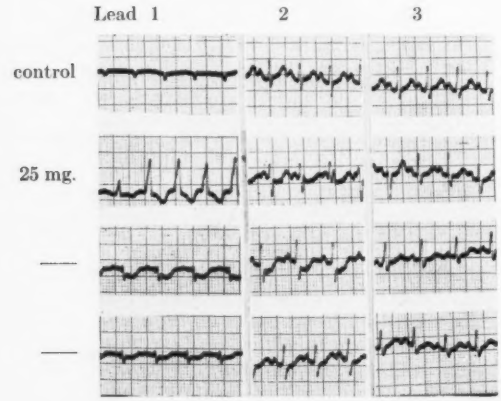

FIG. 4. After 25 mg. of Enzar, there were transient conduction defects, followed by the development of an R wave in lead I, and S-T depression in leads I and II, with T wave inversion in lead II. The lower strips were recorded 2 and 10 minutes after termination of the infusion. The animal lived.

Sixteen of the animals developed clear-cut changes in the ST-T deflections. These could not be explained on the basis of altered position of the heart in the chest. The usual change

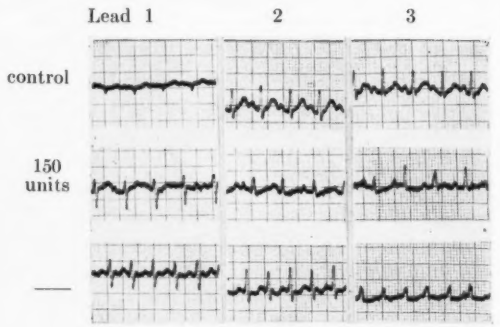

FIG. 5. Administration of 150 units of thrombin produced alteration in the intrinsic structure of the QRS complex with T-wave reversals. The last strip was recorded 37 minutes after the termination of the infusion. The animal lived.

was the development of a marked S-T vector, of variable direction, with definite bowing of the S-T, with concavity frequently directed toward the baseline as in figures 3 and 4. Although the direction of this new vector varied from animal to animal, and sometimes from time to time in the same animal, in general the most common finding was a depression of the S-T segment in lead I, with variation in leads II and III. The T waves showed marked and unpredictable variation in their height, direction, and shape. The Q-T interval was in general limited by the appearance of the P wave of the following beat, but the general impression gained from inspecting these records is that the Q-T interval was frequently prolonged. Figure 1 illustrates a complex of alterations which occurred in variable amount in a number of the animals. The T wave assumed the form of a straight, oblique line, which rose during the inscription of the complex, until finally it fused imperceptibly with the P wave of the following complex.

The rate usually remained unchanged during and after the administration of the enzyme. In a number of instances, relative bradycardia with persistence of the sinus mechanism was recorded; figure 2, however, illustrates the appearance of a brief run of relative tachycardia. Shift of the pacemaker is shown in figure 3, while figure 4 showed the appearance of an electrical syndrome resembling the Wolff-Parkinson-White syndrome.

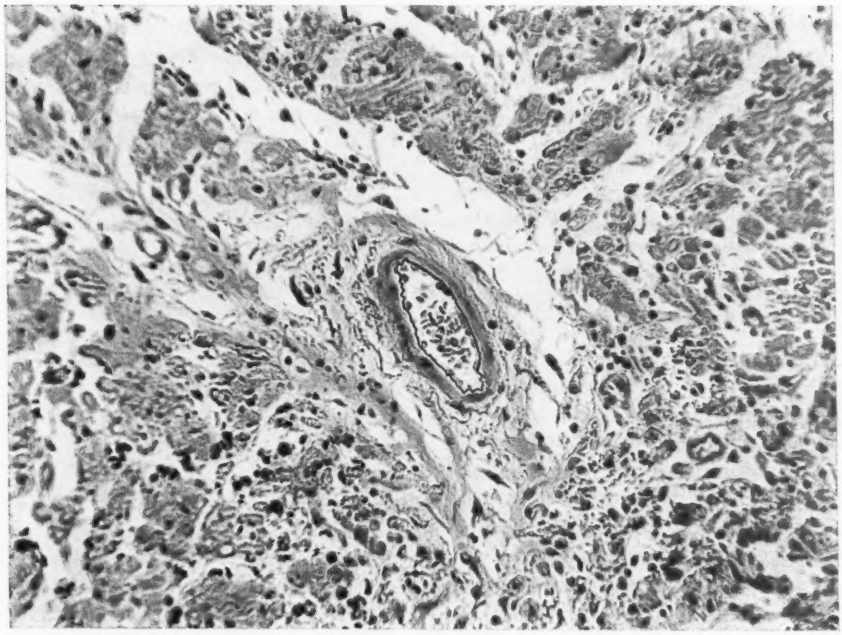

PLATE I. Photograph of the left ventricular myocardium of a rabbit. This animal was sacrificed 48 hours after trypsin, 25 mg. in normal saline, was administered by slow intravenous drip. The section shows an area of necrosis of myocardial fibers, in the center of which lies a patent arteriole, with no evidence of thrombosis. H & E stain by courtesy of Dr. Aaron Kellner.

A number of the animals either actively convulsed, or emitted several loud cries. At this time they ceased to breathe, and corneal and other reflexes, previously obtainable, were no longer elicited. At this time, there abruptly appeared a rather characteristic electrocardiogram. There was marked bradycardia, with extreme prolongation of the P-R, QRS and Q-T intervals. Marked conduction defects were frequently present, and there was often either complete A-V dissociation, or marked downward shift of the pacemaker. In every one of these animals, the changes persisted with the beats becoming less frequent and of persistently lower voltage, until finally no electrical activity was elicited. These characteristic signs were clearly distinct from the previously described alterations. They are similar to terminal electrocardiograms in the human, as described by Turner.[5]

Four rabbits were given infusions of thrombin. Three of them died after convulsions, and terminal records similar to those described in the preceding paragraph were obtained in two. Earlier in the course of the administration, changes in the intrinsic form of the QRS and S-T displacements were recorded in two of the four animals, which were clearly distinguishable from the A-V dissociation, marked bradycardia and idioventricular rhythm of the preterminal records (fig. 5).

DISCUSSION

These data suggest that the administration of intravenous trypsin in the dosage described is usually accompanied by alterations in the electrical activity of the rabbit's heart. These are much greater than the spontaneous variations reported by Levine.[4] There can be little doubt that administration at these levels is accompanied by some intravascular thrombosis, and it would appear likely that some emboli reach the heart or lungs and are responsible for some of the electrocardiographic abnormalities. However, administration of thrombin in doses which were sometimes sufficient to

render the blood completely incoagulable in a small group of animals, appeared capable of producing only a part of the electrocardiographic changes which the proteolytic enzyme produced. This suggests that some action, other than the known thrombus-producing one, is involved. The work of Kellner and Robertson casts considerable light on this problem. They showed that the intravenous infusion of trypsin or of papain produced "focal areas of necrosis of muscle fiber, distributed throughout both ventricles, and having no relationship to blood vessels." (See plate I.) A small group of heparinized animals in their series appeared to give a similar response.

In the data reported here, a number of dramatic and precipitous electrocardiographic changes are shown. Some of them are short-lived. This would suggest that limited episodes of impaired intracellular metabolism or of local thrombosis might produce transient functional blocks in the Purkinje system which would account for both the appearance of conduction defects in the usual sense, and the appearance, in several of the rabbits, of a complex compatible with the Wolff-Parkinson-White syndrome. The implication that "accelerated conduction"[6] has appeared, is worthy of consideration in these records. The T-wave alterations are compatible with random myocardial damage, and the marked S-T displacements indicate that certain randomly distributed areas of epicardium have been severely injured. The P-wave alterations suggest diffuse damage of the auricular myocardium.

It would appear, therefore, that the intravenous administration of trypsin produced changes in the electrocardiogram of the rabbit, which may be due to a direct effect on intracellular metabolism, or the thrombogenic activity of trypsin, or to both.

Summary

An aqueous solution of trypsin was infused into anesthetized rabbits. It produced marked changes in the rhythm, and alteration in the P, QRS, S-T and T deflections of the electrocardiogram. These were distinct from the characteristic changes in the electrocardiogram of the dying animal. Changes which were generally similar, but of a much less marked degree, were produced in a small number of animals which received intravenous thrombin.

Sumario Español

Una solución aquosa de tripsina fué administrada a conejos anestesiados. Produjo marcados cambios en el ritmo y alteraciones en la P, QRS, S-T y deflecciones T del electrocardiograma. Estos fueron distintos a los cambios característicos en el electrocardiograma de un animal moribundo. Cambios que generalmente fueron similares, pero de mucho menor grado, fueron producidos en un número reducido de animales que recibieron trombina intravenosa.

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Pulmonary Arteriosclerosis and Cor Pulmonale Due to Recurrent Thromboembolism

By P. J. Barnard, M.D., M.R.C.P.(E)

A long-term experiment will be described which has shown that repeated injections of minute autogenous blood clots in rabbits caused pulmonary arteriosclerosis and cor pulmonale. Pulmonary arterial lesions were of two main kinds with respect to circumference of the intimal coat: eccentric, ascribable to intimal incorporation of clot, and circumferential, probably ascribable to hypertension and vasospasm. A counterpart to this animal experiment is probably to be found in human pathology, as suggested by certain case reports, by the pathology of lymphangitis carcinomatosa and by evidence that circulating blood is not clot free.

EVIDENCE has now accumulated that incorporation of blood clot into arterial intima might as well be a cause as a result of arteriosclerosis. Those who have studied large human systemic arteries from this thrombogenic viewpoint agree that all aspects of intimal arteriosclerosis including atheroma can follow incorporation of blood clot.[1-4] Because red cell envelopes are rich in lipoid, it is suggested that their breakdown supplies much of the fatty material in arteriosclerosis.[1, 5] Experiments on the effects of blood clot emboli in pulmonary arteries, though showing that fibrous and elastic tissue form intimally, have not produced atheroma.[6-9] It is, however, possible that pulmonary arteries might differ from systemic arteries in their response to blood clot. (Pulmonary artery pressure is much lower than systemic pressure and pulmonary arteries transport venous blood.) Also, atheroma is exceedingly rare in veins. Furthermore, because atheroma both in pulmonary and systemic arteries is mostly limited to large elastic branches, this disease was perhaps not to be expected because the blood clot emboli used experimentally were far too small to lodge in vessels the size of elastic arteries.

The following experiments were undertaken to study afresh the effects of blood clot on the pulmonary arteries, and it is argued that thromboembolism could account for some human cases in which arteriosclerosis largely confined to pulmonary arteries is associated with cor pulmonale.

From the Institute for Pathology, Pretoria, South Africa.

Material and Methods

Twenty *young* fullgrown rabbits of various colors and both sexes, weighing 2.4 to 3.7 Kg. were used. Sixteen received fibrin emboli and four red clot emboli.

Preparation of Emboli

Fibrin emboli were prepared as follows: By incising marginal ear vessels with a safety razor blade, 1.6 ml. of blood was collected in a tube containing 0.2 ml. of 3.8 per cent sodium citrate solution. After spinning this blood at 2,500 revolutions per minute for five minutes, the plasma was pipetted into 10 ml. of calcium chloride, 0.025 molar solution. The clot that formed was dipped in physiologic saline, transferred to a petri dish and moulded with a glass rod flattened at one end to a disc lying in a pool of serum. The serum kept fibrin fragments together while they were chopped fine with a safety razor blade, a maneuver easily completed in 60 seconds. After tilting the dish slightly, chopped up fragments were washed to the edge (by squirting 2 ml. of normal saline through a needle) whence they were aspirated directly through the syringe nozzle. (With practice, few fragments failed to reach the barrel.) Fibrin so prepared was then injected into an ear vein. This dose of fibrin, which is the amount contained in 1.6 ml. of blood, was administered twice weekly on Mondays and Thursdays, though on several occasions a week, and once, a month elapsed between injections. Each rabbit received fibrin from its own blood. To preserve veins, ears were used alternately for bleeding and injection, injections being carried out as distally as possible and preferably through the previous puncture mark. Ear incisions were also made through or close to previous incisions. Such precautions make it possible to bleed from and inject marginal veins almost indefinitely. After each rabbit had been given 10 injections, rabbits 5 and 13 were killed to find out if arterial lesions had been produced. From sections of their

TABLE 1.—*Experimental Rabbits (20)*

Rabbit No. and sex	Kind of emboli	Number of doses	Time during which emboli were injected (days)	Time lapse between last injection & death (days)	Mode of death
1 M	Fibrin	35	200	150	Killed to end experiment.
2 F	Fibrin	35	200	150	Killed to end experiment.
3 F	Fibrin	70	368	62	Killed to end experiment.
4 M	Fibrin	35	200	150	Killed to end experiment.
5 F	Fibrin	10	80	3	Killed for control.
6 F	Fibrin	35	200	150	Killed to end experiment.
7 F	Fibrin	35	200	3	Cor pulmonale.
8 F	Fibrin	16	106	9	Paralyzed. Died.
9 M	Fibrin	65	346	2	Cor pulmonale.
10 M	Fibrin	70	368	5	Cor pulmonale.
11 F	Fibrin	15	102	13	Conjunctivitis-killed.
12 M	Fibrin	35	200	150	Killed to end experiment.
13 F	Fibrin	10	80	3	Killed for control.
14 M	Fibrin	70	368	20	Cor pulmonale.
15 M	Fibrin	35	200	150	Killed to end experiment.
16 F	Fibrin	70	365	62	Killed to end experiment.
17 M	Red clot	60	318	62	Killed to end experiment.
18 F	Red clot	60	318	62	Killed to end experiment.
19 M	Red clot	60	318	62	Killed to end experiment.
20 F	Red clot	60	318	62	Killed to end experiment.

lungs it seemed likely that induction of extensive obliterative vascular disease would require many more injections. After 15 injections rabbit 11 developed fulminating conjunctivitis for which it had to be destroyed 13 days later. It received no more injections during this time. Another animal rabbit 8, which was found paralyzed in its hindquarters after the sixteenth injection, died nine days later, but postmortem examination failed to establish the cause. None of these four had developed cor pulmonale. Three days after each animal's thirty fifth injection rabbit 7, breathless for some 14 days, died. The cause was established as pulmonary arteriosclerosis and chronic cor pulmonale. At this stage the remaining animals, all outwardly normal, were divided into two groups. The first group, consisting of six animals (rabbits 1, 2, 4, 6, 12 and 15), was set aside and received no more fibrin. These rabbits were killed 150 days later, and though all had developed pulmonary arteriosclerosis, none had cor pulmonale. The second group, consisting of 5 animals (rabbits 3, 9, 10, 14 and 16), was injected as before. At the sixty fifth injection respiratory distress was present in all for some 30 minutes or so following injection, though in rabbit 9 alone was discomfort severe. It died two days after the sixty fifth injection from chronic cor pulmonale. The remaining four (rabbits 3, 10, 14 and 16) were then given five more injections each. Rabbits 10 and 14 died 5 and 20 days, respectively, after the seventieth injection from cor pulmonale. Rabbits 3 and 16, after being allowed to run about in a large room for two months, were killed. The number and kind of injections each animal received, length of time during which fibrin fragments were injected and the time lapse between the final injection and death of each animal are summarized in table 1.

Red blood clot emboli were prepared from 0.75 ml. of autogenous blood allowed to clot spontaneously. After retraction the clot was chopped up and injected at the same time intervals as for rabbits receiving fibrin. As one rabbit of the four became slightly distressed following 15 injections, all subsequent doses of red clot fragments were prepared from 0.5 ml. of blood. This latter dose was chosen only because it caused no obvious distress. These rabbits received 60 injections each. Respiratory distress was only observed after the final few injections each rabbit received. They were then allowed to run about for two months before they were killed.

Measurement of Fibrin Fragments

Fibrin fragments prepared from each of 10 control rabbits were discharged on glass slides and the coverslips ringed with grease. Greatest diameters only of the first 100 fragments encountered on each slide were then measured using an eyepiece micrometer, and the 1,000 fragments classified into the size ranges: greater than 1.0 mm., 1.0 to 0.1 mm. and less than 0.1 mm. Their percentage size distribution is set out in table 2, as is the distribution in the same size ranges of the 3,488 arterial lesions found in sections prepared from the lungs of experimental animals. The purpose of this is discussed under Results.

Arterial Circumferences and Ventricular Weights

Twenty healthy rabbits of various colors, both sexes, and at least 1 year old, to correspond with the

TABLE 2.—*(Rabbits 1–16) Correspondence between Size Distribution of Fibrin Emboli and Incidence of Arterial Lesions in the Same Size Ranges*

	>1.0 mm.	1.0 to 0.1 mm.	<0.1 mm.
Fibrin emboli (1000).....	3%	59%	38%
Arterial lesions (3488)....	1%	68%	31%

TABLE 3.—*(20 Control Rabbits and 20 Experimental Rabbits) Arterial Circumferences and Ventricular Weights*

Rabbit No.	Arterial circumferences (mm.)		Right ventricle × 100 / Left ventricle + Septum
	Aorta	Pulmonary artery	Gm. %
Control rabbits (20)			
1	10	12	23.29
2	12	15	24.33
3	11	11	24.30
4	13	12	25.47
5	13	13	25.34
6	12	14	24.61
7	13	15	24.06
8	14	13	24.06
9	12	13	24.81
10	15	15	26.09
11	15	15	25.00
12	14	16	25.29
13	13	13	26.04
14	13	15	24.44
15	11	12	24.55
16	12	14	24.44
17	11	12	24.37
18	12	14	25.75
19	12	15	23.26
20	13	10	25.39
Mean	12.5	13.4	24.74
SD	0.54	1.97	0.09
Experimental rabbits without cor pulmonale (10) fibrin			
1	15	13	20.03
2	15	16	24.90
4	14	16	24.02
5	11	13	23.70
6	16	18	25.05
8	11	14	25.31
11	10	14	24.20
12	12	14	22.27
13	14	13	24.60
15	14	16	25.76
Mean	13.2	14.7	23.98
S D.	2.0	1.7	1.7
Experimental rabbits with cor pulmonale (6) fibrin, (4) red clot			
3	15	18	31.01
7	12	23	50.07
9	14	18	50.51
10	16	20	34.79
14	14	22	36.09
16	14	17	29.62
17	14	18	33.78
18	13	16	31.85
19	15	15	34.50
20	12	14	35.85
Mean	13.9	18.1	36.61
SD	1.3	2.8	7.4

$$\text{Standard Deviation} = \sigma\sqrt{\frac{n}{n-1}}$$

age of the experimental animals at the time of death, were kept under the same conditions as experimental rabbits. They were then killed and their hearts, lungs, kidneys and livers removed. After fixing for four days in 4 per cent neutral formaldehyde solution, the hearts were dissected by the method of Fulton and coworkers,[10] ventricles being weighed separately. Because the right ventricle is relatively thin and joins the interventricular septum at about right angles, it could be dissected free with some accuracy; not so, however, the left ventricle, which is relatively much thicker and merges imperceptibly with the septum at an acute angle. For this reason right ventricular weight has been expressed as a percentage of septal and left ventricular weights combined. Narrow rings were cut from aorta and pulmonary artery immediately above their respective cusps, severed, and measured lying flat on a millimeter scale. Ventricular weights and arterial circumferences in control and in experimental animals are listed in table 3.

Measurement of Right and Left Ventricular Blood Pressures

This was done in 10 normal rabbits, five with and five without intravenous Nembutal anesthesia. Pressures were secured by direct ventricular puncture, using a Sanborn electromanometer and direct writing recorder. Since anesthesia was found to effect changes in right ventricular pressures only slightly, the experimental animals were studied without an anesthetic. An attempt was made to measure pressures in both ventricles, as the pressure difference was used to confirm that the right ventricle had actually been

TABLE 4.—*Right Ventricular Blood Pressures (mm. Hg) in Control and Experimental Rabbits*

Controls (10)				Experimental rabbits (12)						
No.	Systolic	Diastolic	Mean	No.	Systolic	Diastolic	Mean	*CP	No. of doses	Time interval after final injections at which readings were taken (days)
1	33.0	0	19.0	1	29.0	0	12.0		35	160
2	37.0	0	10.0	2	31.0	0	14.4		35	160
3	22.0	0	9.2	3	24.0	0	12.0	+	70	62
4	31.5	−7	11.0	6	29.0	0	14.4		35	160
5	30.0	0	13.5	10	32.0	?	11.5	+	70	2
6	27.0	0	12.0	12	26.0	0	7.2		35	160
7	24.0	0	11.0	14	84.0	+2.4	36.0	+	70	2
8	21.0	−4	5.4	15	21.5	+2.4	11.0		35	160
9	21.5	−2.7	11.0	16	24.0	0	12.0	+	70	62
10	27.0	+2.7	13.5	17	21.0	+4.8	12.0	+	60	62
				19	39.0	0	17.0	+	60	62
Mean	27.4	−1.1	11.5	20	95.0	0	35.0	+	60	62
S.D.	5.02	7.07	3.35							

$$\text{Standard Deviation} = \sigma\sqrt{\frac{n}{n-1}}.$$

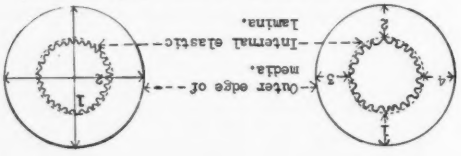
* CP: Cor Pulmonale

entered. Only right ventricular pressures appear in table 4.

Measurements

Medial thickness of pulmonary arteries was measured both in control and experimental animals, using preparations stained with Weigert-van Gieson. The method is summarized diagramatically:

(a) *Medial thickness* (Mean of 1, 2, 3 and 4) (*b*) *External diameter* (Mean of 1 and 2)



Mean medial thickness (a) was expressed as a percentage of mean external diameter (b). Only arteries with circular or nearly circular outlines were measured. Because arteries exhibited varying amounts of contraction as judged by degree to which the internal elastic lamina was corrugated, true medial thickness was taken to be the distance between troughs of corrugations and outer edge of the medial coat. A total of 100 sections from different parts of the lungs of 14 control rabbits was used to measure the first 100 arteries encountered in cross section in each of the size ranges 1.0 to 0.1 mm. and less than 0.1 mm. external diameter. Arteries larger than 1.0 mm. were so few as to make measurement impracticable. By comparing these with similar measurements in fibrin-injected animals it was hoped to discover if medial hypertrophy had resulted from recurrent thromboembolism. Similar measurements were not made on red-clot injected rabbits because they were too few in number. Fibrin-injected animals were divided into those with and those without right ventricular hypertrophy. All pulmonary arterial lesions encountered in cross section in lung sections of these two groups were measured and classified into the same size ranges as for controls. This was done to find out if there was any difference in medial thickness of pulmonary arteries in animals that had developed cor pulmonale and also if any difference affected arteries of one size range only. The number of vessels in each size range measured in control and experimental rabbits as well as the results are recorded in table 5.

Classification of Arterial Lesions

The 1,859 pulmonary arterial lesions encountered in the lung sections of rabbits with cor pulmonale were classified into size ranges: greater than 1.0 mm., 1.0 to 0.1 mm. and less than 0.1 mm., and into the types of lesion listed in table 6. In rabbits without cor pulmonale 1,629 arterial lesions were similarly classified.

Fibrinolytic Activity in Peripheral Blood

This was tested for by the method of MacFarlane and Pilling.[11] Blood samples were withdrawn by cardiac puncture in five groups each consisting of two control rabbits, at time intervals of ½, 1, 2, 6 and 24 hours, respectively, after injection of fibrin

fragments prepared from 1.6 ml. of blood. In a further five groups, each consisting of two control rabbits, autogenous red clot fragments prepared from 0.5 ml. of blood were injected and blood samples withdrawn for examination at the same time intervals as before. These experiments showed that emboli of either kind did not produce detectable fibrinolytic activity in peripheral blood.

TABLE 5.—(*Rabbits 1–16*) *Medial Thickness of Pulmonary Arteries in Control and Experimental Rabbits Expressed as a Percentage of External Diameter*

	No. of Arteries measured	Means	Standard Deviations	Standard errors of differences between means
Control rabbits (14)				
Arteries <0.1 mm.....	100	6.2	1.5	
Arteries 0.1–1.0 mm....	100	12.5	6.3	
Rabbits without cor pulmonale (10)				
Arteries <0.1 mm.....	101	6.9	4.1	0.434
Arteries 0.1–1.0 mm....	103	12.4	6.2	0.877
Rabbits with cor pulmonale (6)				
Arteries <0.1 mm.. ...	73	4.2	0.7	0.171
Arteries 0.1–1.0 mm.. .	84	7.6	5.2	0.847

Standard error of difference between means = $\sqrt{\frac{\sigma_c^2}{n_c} + \frac{\sigma_e^2}{n_e}}$

c stands for control animals

e for experimental animals

Preparation and Staining of Sections

Lungs, kidneys and livers both of control and of experimental rabbits were fixed in 4 per cent neutral formaldehyde solution. Lower lobes of lungs were each divided into three portions, but other lobes were embedded whole. All sections were stained with Weigert–van Gieson and sometimes hematoxylin-eosin as well. Frozen sections from the lungs of rabbits that had received fibrin injections were stained for fat with Sudan III and compared with similar sections from rabbits that had received red clot injections.

RESULTS

Rabbits 1–16: Fibrin Emboli

Rabbits Without Cor Pulmonale: (Rabbits 1, 2, 4, 5, 6, 8, 11, 12, 13 and 15.) All rabbits that had received 35 injections or less (except rabbit 7) showed no abnormality at postmortem examination apart from the lungs; though outwardly normal, their cut surfaces were studded with thickened arteries. Circumferences both of aorta and pulmonary artery were within normal limits. Right ventricular pressures of rabbits in which tracings were secured were within the normal range four months after final injection of emboli and one month prior to killing (table 4). Microscopic examination revealed extensive arteriosclerosis, but as pulmonary arterial lesions were similar in structure to those in animals with cor pulmonale, no separate description of them will be given here.

TABLE 6.—(*Rabbits 1–16*) *Incidence of Arterial Lesions*

Types of lesion	>1.0 mm.		1.0 to 0.1 mm.		<0.1 mm.		Totals		Percentage	
	With *CP	Without CP	With CP	Without CP	With CP	Without CP	With CP	Without CP	With CP	Without CP
Circumferential intimal fibrosis	7	4	277	265	170	139	454	408	24.4	25.1
Eccentric intimal fibrosis	8	2	168	183	69	89	245	274	13.2	16.8
Circumferential fibro-elastic thickening	5	2	289	236	99	152	393	390	21.1	23.9
Eccentric fibro-elastic thickening	6	16	185	184	30	167	221	367	11.9	22.5
Medial scarring	0	0	182	75	61	9	243	84	13.1	5.2
Recanalization	1	4	252	87	50	15	303	106	16.3	6.5
Totals	27	28	1353	1030	479	571	1859	1629	100.0	100.0
Grand totals and percentages	55 or 1%		2383 or 68%		1050 or 31%		3488 or 100%		1859 or 100%	1629 or 100%

* CP: Cor Pulmonale.

Rabbits with cor pulmonale: (Rabbits 3, 7, 9, 10, 14 and 16.) All rabbits that had received 70 injections each (rabbits 3, 10, 14 and 16), one rabbit that had received 65 (rabbit 9) and one that had received 35 (rabbit 7) showed cor pulmonale at postmortem examination. Of these, rabbits 7, 9, 10 and 14 died from cor pulmonale, but rabbits 3 and 16 were killed 62 days after their final injection. Cor pulmonale, which was diagnosed by the naked eye in these six as well as in the four rabbits (rabbits 17, 18, 19 and 20) that received red clot emboli, is also reflected in the figures for right ventricular weights, all of which were above normal (last column of table 3). However, only rabbits 7 and 9 had pronounced right ventricular hypertrophy. Though the mean pulmonary arterial circumference reflects dilatation in animals with cor pulmonale as a group, dilatation was obvious to the naked eye only in rabbits 7 and 14, both of which died from cor pulmonale. The high mean value is attributable mainly to the measurements from these two animals.

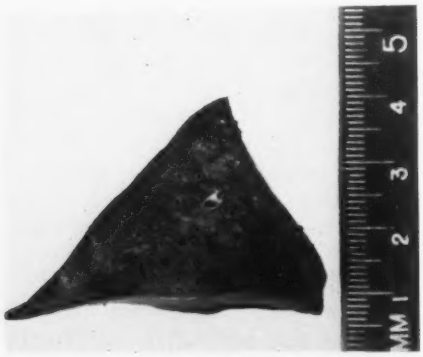


FIG. 1. Rabbit 14. Lower lobe of left lung showing prominence of divided arteries. (Approximately life size.)

FIG. 2. Rabbit 7. Hypertrophy of right ventricle and dilatation of pulmonary artery. (× 4 approximately.)

Right ventricular pressures were secured in the rabbits listed in table 4. Only rabbits 14 and 20 (readings taken two days after the seventieth injection of fibrin emboli and 62 days after the sixtieth injection of red clot emboli respectively) had marked elevation of right ventricular systolic and mean pressure.

In rabbits that eventually died from cor pulmonale (rabbits 7, 9, 10 and 14), but especially the first two (both of them albinos) skin and mucous membranes were found to be so blue that they could have been called "black cardiacs." Polycythemia was evident because the supernatant layer of plasma after spinning down citrated blood for preparation of emboli was far narrower than it had been at the beginning of the experiment.

Animals dying from cor pulmonale (except rabbit 10) in contrast to rabbits 13 and 16, in which right ventricular hypertrophy without signs of failure was found on killing, also showed ascites, bilateral hydrothorax, in one animal (rabbit 7) hydropericardium, and passive venous congestion of the abdominal viscera. In all animals pleural lung surfaces were normal, but cut surfaces showed widespread thickening of arteries (fig. 1). Apart from passive venous congestion, organs other than heart and lungs appeared normal. Right ventricular hypertrophy is illustrated in figure 2.

Microscopic appearances of lungs. (Rabbits 1–16.) *Arteries.* Classification of the 3,488 arterial lesions showed that they were most numerous in arteries 1.0 to 0.1 mm. in external diameter (68 per cent), next numerous in arteries less than 0.1 mm. (31 per cent) and least numerous in arteries greater than 1.0 mm. (1

per cent). Size distribution of fibrin emboli also shows that they were likely to have lodged in about the same proportions in arteries of these size ranges (table 2). This correspondence does not necessarily mean that lesions were brought about by intimal incorporation of fibrin. Thus lesions due to vasospasm would also be most numerous in arteries of that size range in which most emboli became impacted.

Arterial lesions (1,859 in animals with and 1,629 in animals without cor pulmonale) were classified as follows: (a) Circumferential intimal fibrosis (endarteritis obliterans or endarteritis fibrosa) (figs. 4, 6, 7, 9 and 10). Compare with the contracted though otherwise normal vessels in figures 3 and 5. (b) Eccentric intimal fibrosis (figs. 11 and 12). (c) Circumferential fibroelastic intimal thickening which included elastosis (figs. 14, 15 and 16). (d) Eccentric fibroelastic intimal thickening (fig. 17). (e) Medial scarring (fig. 13). (f) Recanalization (fig. 18).

"Circumferential" meant that a lesion was present all around the intimal periphery. Lesions of this type had inner contours that were either smooth (figs. 7, 8, 9, 14, 15 and 16) or scalloped (figs. 4, 6 and 10). "Eccentric," on the other hand, meant that intimal thickening was present at one or more places on the intimal circumference, the rest of the intima being normal (figs. 12 and 17). The term "fibrosis" signified that elastic tissue either was wholly absent or present only in small amount (figs. 6, 7 and 10), and the term "fibroelastic" that new elastic tissue and fibrous tissue were present in about equal amounts (fig. 14). For purposes of classification this term also included less frequent lesions depicted as "elastosis" (figs. 8, 15 and 16), which were composed of elastic laminae set concentrically and in which van Gieson's stain revealed little collagen. "Medial scarring" (fig. 13) referred to segmental replacement of muscle by collagen, and "recanalization," partition of vascular lumens by septa consisting either of fibrous or fibroelastic tissue (fig. 18). Very occasionally a compartment showed formation of a new intraluminal artery complete with muscular media and internal elastic lamina. Reference to table 6 shows that the relative proportions of lesions classified as circumferential intimal fibrosis, eccentric intimal fibrosis and circumferential fibroelastic thickening in arteries of the three sizes taken together were about the same whether or not cor pulmonale was present. Medial scarring and recanalizations were, however, proportionally at least twice as numerous, and eccentric fibroelastic intimal thickening only half as numerous in animals with cor pulmonale as in the rest. Though these results seem to be significant, I cannot explain them because factors such as vasospasm, hypertension and possibly hypoxemia, which it will be argued caused most vascular damage, are so complexly interrelated.

Analysis of table 5 shows that there was no medial hypertrophy of pulmonary arteries in the 10 rabbits without cor pulmonale and that atrophy was actually present in rabbits with cor pulmonale. Because arterial media was often very thin, especially in arteries of less than 0.1 mm., medial thickness in these rabbits was even less than figures show. Even though some of this medial "thinning" was due to arterial dilatation, figures are not vitiated, because this contingency was allowed for by the method adopted in taking measurements. Medial thinning was doubtless also favored by the weakening effect of the transmedial vascularization observed in larger arteries at sites opposite intimal thickenings. Though a thin medial coat was sometimes associated with scarring, it most often just "faded" away, a process accompanied by loss of staining affinity (figs. 15, 17 and 18). Slight increase of adventitial collagen was present in some arteries with medial scarring. There was no kind of arterial lesion distinctive among animals with cor pulmonale.

Fat staining showed no sudanophilic material in any arterial lesion. Fibrin emboli undergoing organization were found in the lungs of all animals that died or were killed 20 days or less after the last injection. Some of these lesions were infiltrated by more neutrophils than uncomplicated organization alone could be expected to cause. No eosinophil infiltration was present, and no abscess formation. The lesion was not considered to be a foreign body reaction as in a previous thromboembolic

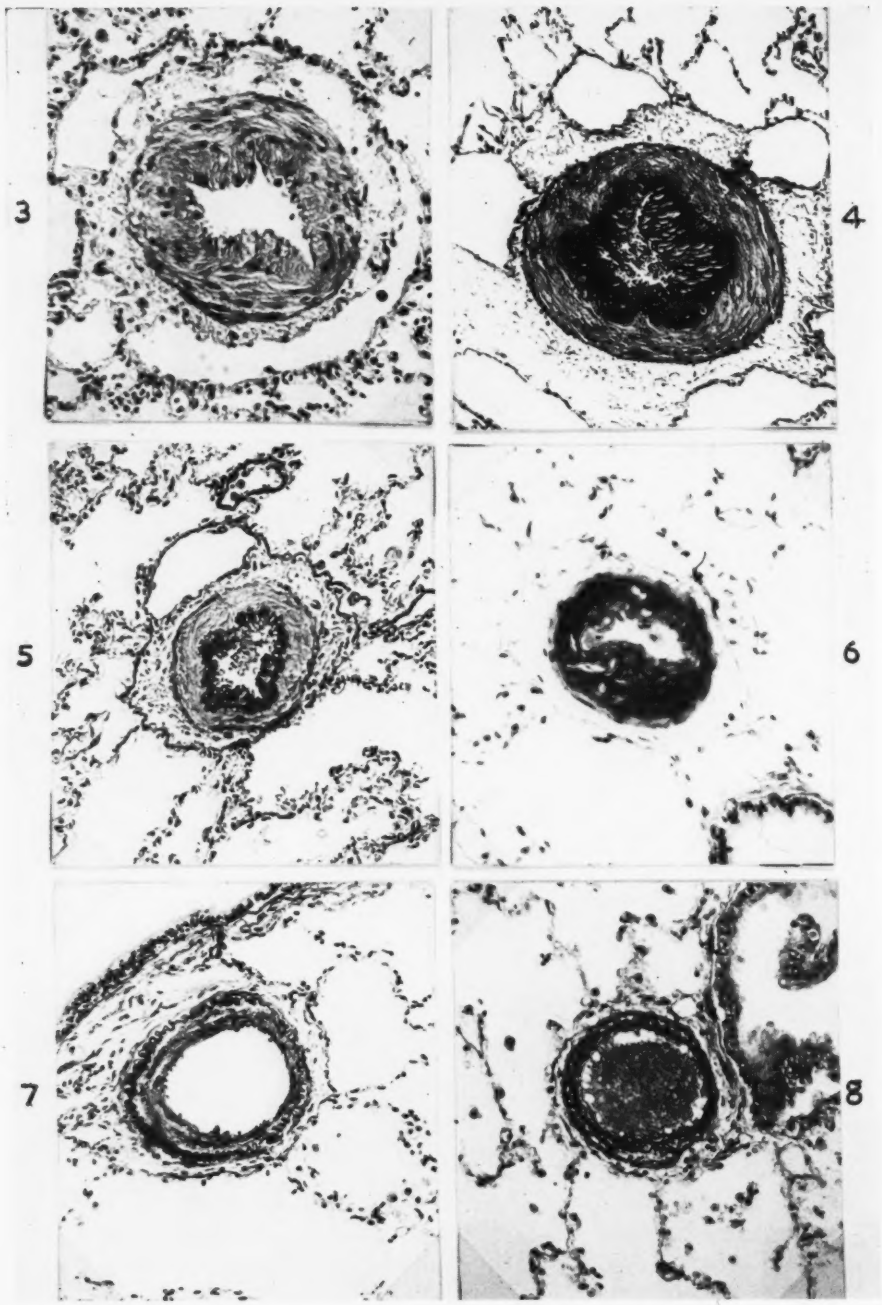


FIG. 3. Control Rabbit 1. Normal contracted artery showing folding of intima and radial arrangement of endothelial cells. (Hematoxylin-eosin × 220.)

FIG. 4. Rabbit 12. Circumferential scalloped intimal fibrosis with radial orientation of collagen at right. (Weigert-van Gieson × 144.)

FIG. 5. Control rabbit 8. Normal contracted artery showing folding of internal elastic lamina. (Weigert-van Gieson × 220.)

FIG. 6. Rabbit 6. Dense circumferential intimal fibrosis (endarteritis obliterans). (Weigert-van Gieson × 275.)

FIG. 7. Rabbit 4. Circumferential intimal thickening with smooth inner contour consisting predominantly of fibrous tissue. (Weigert-van Gieson × 181.)

FIG. 8. Rabbit 2. Minute muscular artery showing elastosis. (Weigert-van Gieson × 275.)

experiment in which fibrin was prepared for injection by grinding.[9] Accidental bacterial contamination might explain these arterial lesions, because fibrin, once prepared, could not be sterilized for fear of altering its properties. Since aseptic precautions were observed, risk of contamination, even during bleeding, cannot have been great. Sensitization to fibrin was improbable, as similar lesions had been found in rabbits receiving autogenous fibrin in a single dose only.[9] No explanation of the rather heavy neutrophilic infiltration of some organizing lesions is, therefore, apparent.

Precapillary vessels, which are endothelial tubes wholly or partially surrounded by an elastic lamina, developed lesions which, though of the same kind in all rabbits, were more numerous in rabbits with cor pulmonale. Endothelial swelling was the mildest change, but was not accompanied by proliferation of the cells. More severe damage was present as eccentric or circumferential formation of a substance reacting pale pink to van Gieson's stain. Such lesions were sometimes accompanied by formation of an additional elastic lamina.

Capillaries were normal except for dilatation in rabbits dying with cor pulmonale.

Veins were normal except in rabbits with cor pulmonale, abnormality taking the form of dilatation and intimal formation of a substance like that in precapillary vessels. No arteriovenous anastomoses were observed in the lungs of any animal.

Bronchial tree and alveolar walls were normal except in animals dying of cor pulmonale, in which alveolar edema was encountered. Interstitial fibrosis was not observed.

Rabbits 17–20: Red Clot Emboli

All showed pulmonary arteriosclerosis indistinguishable from that in rabbits receiving fibrin. Though all four rabbits had cor pulmonale, only rabbit 20 had pulmonary hypertension as well. The finding of cor pulmonale without hypertension in three of them suggests that right ventricular hypertrophy once established from thromboembolism of the lungs, persists, even though pulmonary pressures may return to normal.

Although it was anticipated that lesions induced by red clots would have greater fat content than fibrin-induced lesions, because red cell envelopes are rich in lipoid, this was not so. No rabbit developed atheroma. This, however, does not prove that atherosclerosis cannot be caused by blood clot in systemic arteries.

Arteries of organs other than lungs appeared normal.

The lungs of one control rabbit showed sparsely distributed eccentric intimal fibrosis.

Evidence that Only a Portion of the Blood Clot Injected Was Retained in the Lungs. From the amount of fibrin per dose and the number of injections given, it was calculated that fibrin emboli and red clot emboli from the following total amounts of blood, respectively, were necessary to cause cor pulmonale:

56 ml. . . . . rabbit 7.
104 ml. . . . . rabbit 9.
112 ml. . . . . rabbits 3, 10, 14 and 16.
34 ml. . . . . rabbits 17, 18, 19 and 20.

Thus it was found that cor pulmonale was produced by red clot from a total volume of blood smaller than the volume of plasma needed to produce fibrin clot that would have the same effect. This might be due to the fact that, volume for volume, a greater bulk of clot is to be obtained from whole blood than from plasma. Because of red cell content alone, the amount of red clot obtainable from 34 ml. of whole blood must have been at least half this volume. Such an amount of red clot is large in relation to the capacity of a rabbit's pulmonary arterial tree. It is, therefore, probable that only a portion of the clot given to rabbits 17, 18, 19 and 20 was actually incorporated in pulmonary arterial intima or they would not have survived as long as they did. That the lungs of rabbits do not retain all the red clot injected into them has also been observed by Heard.[12] Except that an intravascular clot in man may "disappear" and that patency of vascular lumens is reestablished after blood clot occlusion by recanalization or by incorporation into arterial intima, nothing definite is known about the fate of thromboemboli. Despite my failure to demonstrate freely circulating fibrinolysin (plasmin) after injection of emboli, it is pos-

sible that fibrinolysis was actually taking place within the lungs and that any fibrinolysin passing into the general circulation was inactivated. Wright and co-workers,[13] who attempted to demonstrate circulating fibrinolysin after producing clots in the ear veins of rabbits, also had no success.

Discussion

If rabbits are given a single dose of fibrin emboli and killed 24 days later, eccentric fibrous tissue intimal thickenings containing new elastic fibers are the only lesions which result in the pulmonary arteries.[9] This kind of lesion has accordingly been ascribed to organization of fibrin into arterial intima; other kinds of lesion in these experimental rabbits must, therefore, have been due to something else. Even supposing that circumferential lesions had resulted from central recanalization of occluding emboli, this explanation would not hold good for development of those nicely concentric elastic laminae illustrated in figures 8, 14, 15 and 16. Hypertension, vasospasm and hypoxemia are other probable mechanisms in the development of such lesions.

A disease such as mitral stenosis which secondarily induces pulmonary hypertension is commonly associated with arteriosclerosis involving intima right around the lumen.[14, 15] Because of this it is thought that hypertension contributed to arteriosclerosis even though only two rabbits had obviously elevated pulmonary blood pressure at time of measurement. In the others, transitory hypertension could have been present following each injection of emboli. Even though hypertension as such cannot be separated from vasospasm in causing circumferential arterial lesions, it is accepted that vasospasm causes hypertension in systemic arteries. Furthermore, numerous studies on early cases of secondary pulmonary hypertension have shown that this form of hypertension also has a reversible element which can be attributed to vasospasm.[16-19] That such vasospasm need not be of central nervous origin is evident from studies on heart-lung preparations.[20, 21] Moreover, pulmonary vasospasm appears to be causatively related to anoxemia. Pulmonary hypertension can be rapidly induced in normal subjects by causing them to breathe 10 per cent oxygen for short periods, the hypertension returning equally rapidly to normal when the low oxygen breathing is stopped. This is attributable to vasospasm.[22] In four cats exposed in a decompression chamber for about two weeks to low oxygen tension in the inspired air, the muscular coats of pulmonary arteries were found hypertrophied.[23] Conversely, it has been shown by von Euler and Liljestrand[24] that in cats the breathing of pure oxygen caused a marked drop in pulmonary arterial pressure. Though it is not known how hypertension and vasospasm bring about arteriosclerosis, it is conceivable that the circumferential lesions which they cause depend upon disturbed arterial nutrition. Rotter[25] and others whom he quotes, believe that arteriosclerosis is produced by defective supply of nutritive lymph to those parts like intima which have no capillaries. This opinion is based upon observation of endarteritis obliterans in the edematous zone of anemic infarcts. It is also maintained that

Fig. 9. Rabbit 7. Loose circumferential intimal fibrosis with smooth inner contour. (Weigert-van Gieson × 181.)

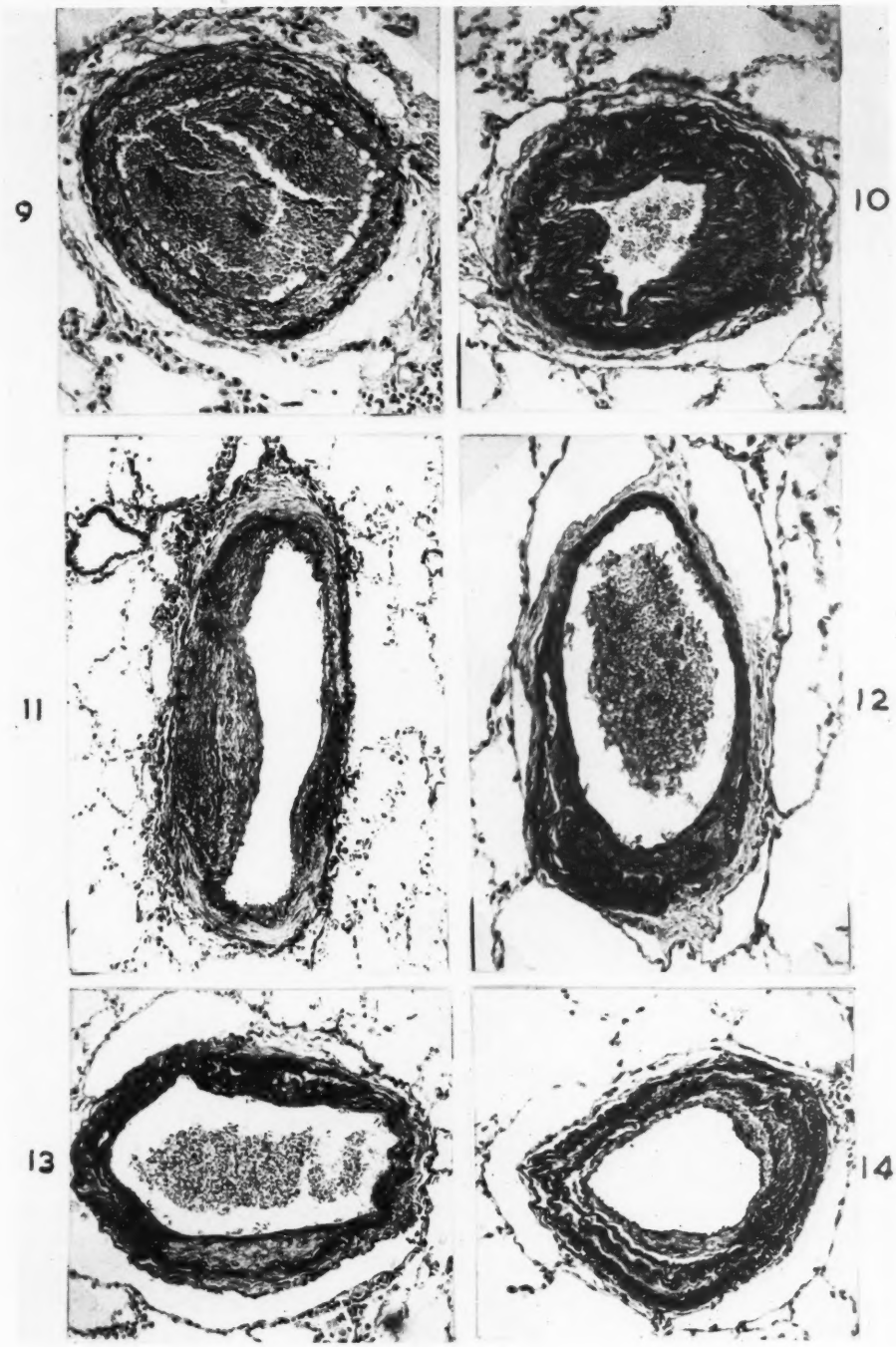
Fig. 10. Rabbit 4. Scalloped circumferential intimal fibrosis with development of new elastic laminae faintly discernable. (Weigert-van Gieson × 181.)

Fig. 11. Rabbit 4. Eccentric, mainly fibrous intimal thickenings. That to the left is partially divided by an elastic membrane suggesting successive incorporations of fibrin. (Weigert-van Gieson × 144.)

Fig. 12. Rabbit 1. Eccentric intimal fibrosis with development of new elastic tissue faintly discernable. Note segmental destruction of internal elastic lamina and media at 5 o'clock. (Weigert-van Gieson × 181.)

Fig. 13. Rabbit 11. A combined circumferential intimal lesion: fibrosis at 6 o'clock with fibroelastic thickening involving rest of circumference. Medial scarring is also present on the left. (Weigert-van Gieson × 144.)

Fig. 14. Rabbit 4. Circumferential intimal thickening composed of fibrous and elastic tissue disposed in alternate layers. (Weigert-van Gieson × 181.)



FIGS. 9–14

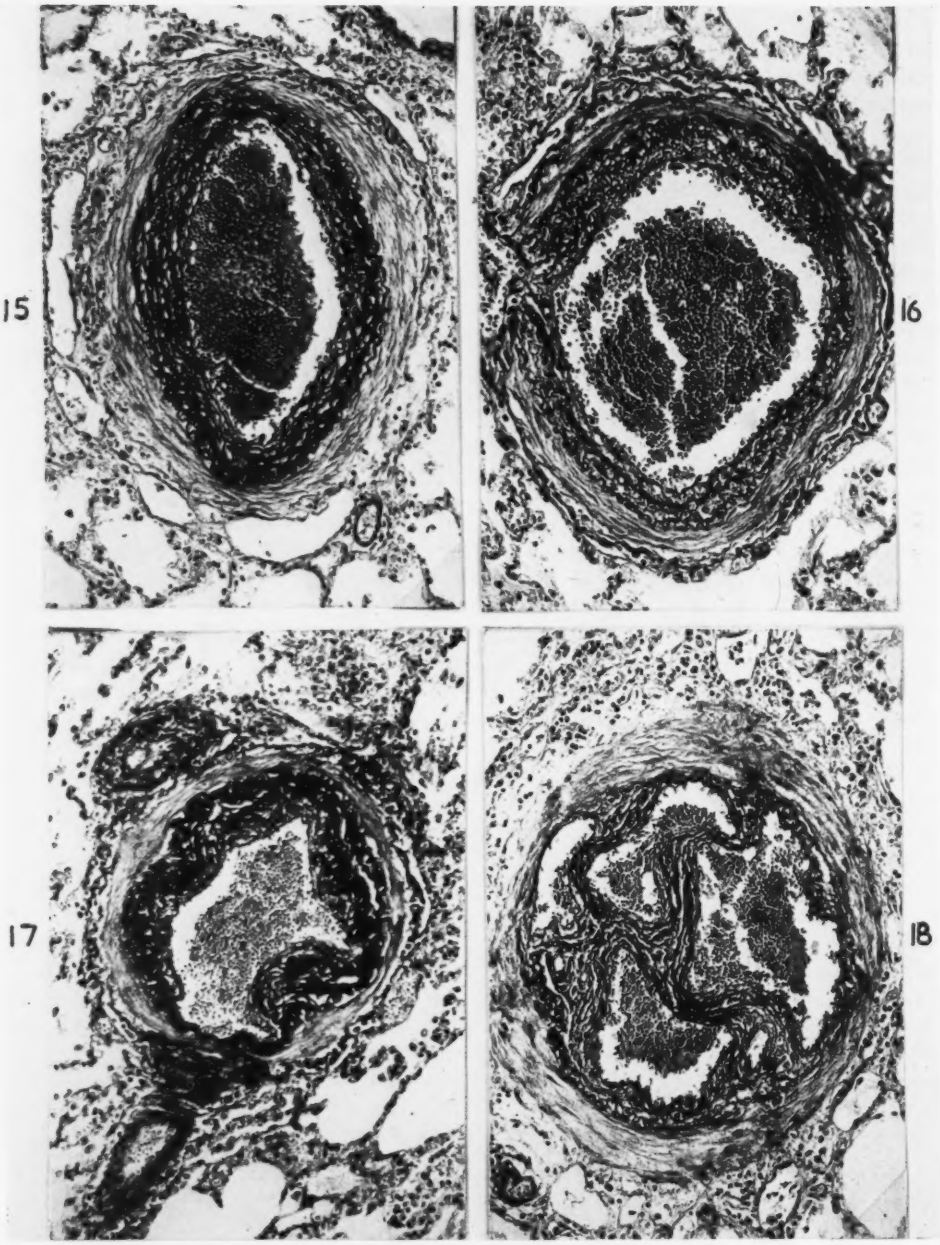


FIG. 15. Rabbit 8. Intimal thickening composed almost wholly of concentric elastic laminae. Animal killed to terminate experiment. No cor pulmonale. (Weigert-van Gieson × 144.)

FIG. 16. Rabbit 7. Elastosis (compare fig. 15). This animal died of cor pulmonale. (Weigert-van Gieson × 144.)

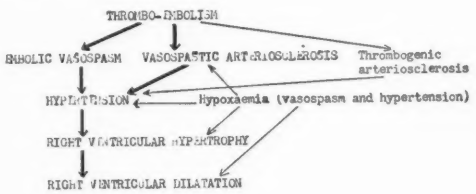
FIG. 17. Rabbit 7. Eccentric fibroelastic intimal thickening: media shows loss of staining affinity. (Weigert-van Gieson × 144.)

FIG. 18. Rabbit 7. Recanalization with fibroelastic septa: note medial loss of staining affinity. (Weigert-van Gieson × 144.)

hypertension, by overstretching arterial walls, embarrasses diffusion of nutritive lymph, so accounting for the well-known association of severe arteriosclerosis with persistent elevation of blood pressure in systemic arteries. de Langen[26] also argues that mechanical interference with nutrition of arterial walls is the primary factor causing arteriosclerosis. It is possible that spasm of small muscular arteries, in contrast to stretching of large elastic arteries, would have the same effect in impairing intimal nutrition. Figures 3 and 5 show contracted pulmonary arteries from normal rabbits with resultant intimal folding and radial instead of parallel arrangement of endothelial cells in respect to arterial circumference. Comparison of these figures with that from an experimental rabbit (fig. 4) showing nodular circumferential intimal fibrosis strongly suggests that spasm had caused this particular lesion. Moreover, radial arrangement of collagen in this figure provides evidence not only that endothelial cells form collagen, but that their orientation determines direction in which this substance is laid down. In similar manner, orientation of fibroblasts in regenerating tendon appears to control the pattern of collagen fibers.[27]

Though hypertension and vasospasm are held to be chiefly responsible for the development of arteriosclerosis in recurrent thromboembolism, it is possible that polycythemia and hypoxemia added their embarrassing circulatory effects, which are hypertension, hypervolemia, and high blood viscosity.[28, 18] Thus rabbit 10 died with right ventricular hypertrophy and dilatation but without transudate in serous cavities, an observation not uncommon in cases of primary pulmonary arteriosclerosis and hypertension. In some case reports of primary pulmonary arteriosclerosis and hypertension, intimal thickening has been regarded as compensatory to congenital medial hypoplasia.[29-32] This interpretation of arteriosclerosis does not, however, fit the present experiment, which has shown that intimal thickening precedes medial atrophy, not the other way about.

I have interpreted the course of events culminating in chronic right ventricular failure as follows: Recurrent embolism by minute blood clot emboli causes eccentric intimal fibrosis. At the same time recurrent vasospasm due to impaction of emboli in arteries then brings about hypertension and impaired intimal nutrition, so that circumferential and concentric lesions consisting not only of fibrous but of elastic tissue also arise. Lesions arising during recurrent embolic vasospastic hypertension remain once they have formed, as in animals, killed five months after the thirty-fifth injection, in which hypertension was absent. Should, however, arteriosclerosis become sufficiently severe or should hypoxemia set in, vasospasm and hypertension, previously recurrent, become continuous. This leads in turn to rapid advance of arteriosclerosis, and thus is a vicious circle established with progressive right ventricular hypertrophy and eventual failure. This complex interrelationship between thromboembolism and cor pulmonale is here set out diagrammatically: heavy arrows indicate that vasospasm was predominant in initiating arteriosclerosis and cor pulmonale; light arrows indicate the effects that thrombogenic arteriosclerosis and hypoxemia might have exerted as well.



If fibrin or red clot embolism occurring over a protracted period is capable of inducing severe pulmonary arteriosclerosis and cor pulmonale in animals which presumably have a normal mechanism of ridding their vessels of clot, the danger must be far greater in those animals or in man in whom this mechanism is defective. This is one reason for thinking that some human cases of primary pulmonary arteriosclerosis need not be a disorder of blood vessels to start with.

Primary pulmonary arteriosclerosis might be a disorder of blood caused by repeated and protracted pulmonary embolism of showers of minute clots from systemic veins where condi-

tions are favorable for intravascular coagulation. If such emboli formed in systemic venous blood, few would pass the pulmonary arterial filter, and thus significant arteriosclerosis would be confined to the lungs. Embolic experiments aimed at discovering the role blood clot plays in causing pulmonary arteriosclerosis would have added significance if lesions could also be brought about by injecting substances which would cause clotting in circulating blood. If rabbits are given repeated intravenous injections of thromboplastin extract either alone[33] or mixed with Russell viper venom,[12, 34] fibrin emboli become arrested in pulmonary arteries and undergo organization resulting in connective tissue intimal thickening sometimes containing new elastic fibers. Other lesions, probably anaphylactic, are encountered at the same time because the coagulants used contained foreign protein. These experiments have the value of demonstrating that sublethal doses of coagulants will cause lesions which, though scanty, are like those found in human cases of pulmonary arteriosclerosis. Schneider[35] has furthermore shown that both placental trauma to rabbits and human *abruptio placentae* can cause acute cor pulmonale from fibrin embolism. Intravascular deposition of fibrin after premature separation of the normally implanted placenta has also been observed by McKay and coworkers.[36]

In 1939, Belt[37] wrote: "It seems to me that stenosing lesions of the pulmonary arterioles may sometimes be caused by minute embolisms occurring perhaps over long intervals." Cases of recurrent thromboembolism with right ventricular hypertrophy have only been recognized when emboli were large, mainly because of their size and because at autopsy their source is easier to demonstrate than that of small emboli would be. But among case reports of recurrent thromboembolism examples may be chosen which illustrate occlusion of pulmonary arteries from the largest to the smallest. Case reports which for example have described embolic occlusion of the main stem or its large branches are those of Belt,[37] Carroll[38] and Petch.[39] Embolism of medium-sized arteries has been described by Castleman and Bland[40] and in a Cabot case report,[41] and embolism of small arteries by Eppinger and Wagner[42] and by Goedel,[43] whose cases showed arteriosclerosis and clots at arterial branching points. Mantz and Craige[44] have described a case of right ventricular hypertrophy ascribable to organization of small thromboemboli widely scattered in small pulmonary arteries where emboli had their source in what was probably a congenital portocaval shunt. Furthermore, it is not unlikely that some cases recorded as primary pulmonary hypertension might have been due to chronic thromboembolism because organizing blood clots were regarded as secondary to the arteriosclerosis. If thrombi are always ascribed to arteriosclerosis, not the other way about, then thromboembolic arteriosclerosis is bound to escape notice.

Chronic cor pulmonale may also be associated with widespread organizing thrombosis of small intrapulmonary arteries due to carcinomatous emboli.[45, 46] In 1947, Saphir[47] wrote, "It is clear that diffuse thickening of the intima, the result of organized mural thrombi, closely resembles and often cannot be distinguished from pulmonary arteriosclerosis." From a case such as that of Schmidt (cited by Brill and Robertson[48]), in which cor pulmonale was due to widespread thrombosis of small pulmonary arteries, cancer cells being encountered nowhere else in the lung except in arteries, it is probable that lymphatic or parenchymal involvement is not necessary for development of arterial lesions. A case of mucoid lymphangitis carcinomatosa without cor pulmonale studied personally showed widespread eccentric intimal fibrosis of small pulmonary arteries (figs. 19, 21, 22 and 23). Intimal thickenings sometimes contained new elastic fibers, but even when elastic tissue was present the collagenous component nearly always predominated. Intimal lesions were associated with varying degrees of distortion and destruction of the intimal elastic laminae (figs. 19 and 23). Some arteries were completely occluded by fibroelastic tissue (fig. 20). The media was usually intact, but in places this layer was scarred and merged with adventitia, which coat sometimes exhibited increase of collagen.

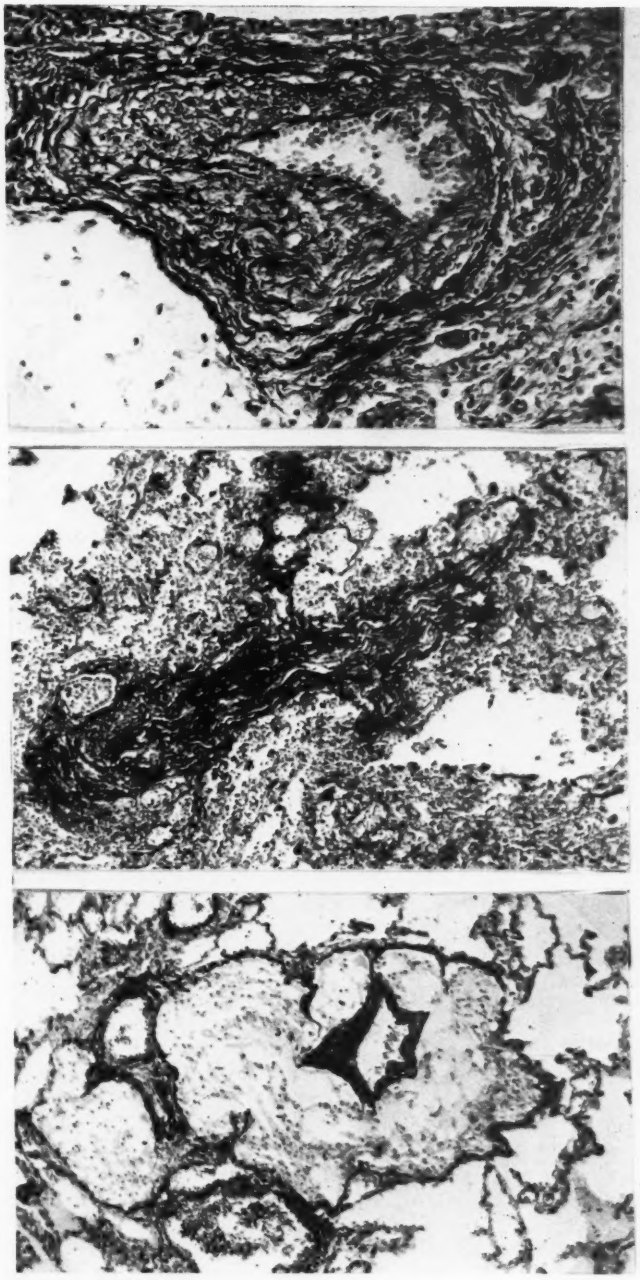


FIG. 19. Human pulmonary artery: Circumferential mainly fibrous intimal thickening. (Weigert-van Gieson × 80.)

FIG. 20. Human pulmonary artery showing fibroelastic obliteration. (Weigert-van Gieson × 80.)

FIG. 21. Human pulmonary artery showing eccentric fibrous intimal thickening: note compression into star-shaped form by surrounding mucoid lymphatic infiltration. (Weigert-van Gieson × 80.)

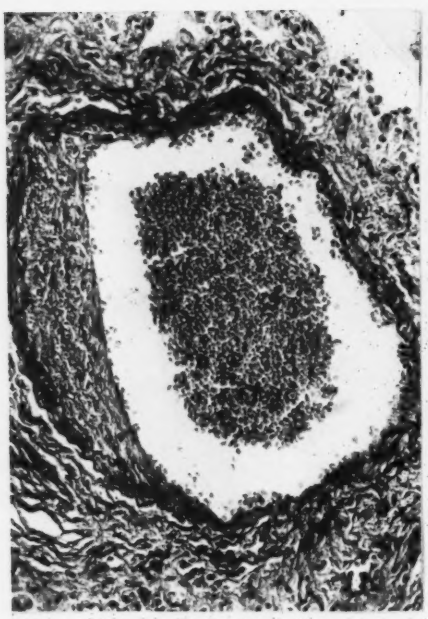


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FIG. 22. Human pulmonary artery showing eccentric fibrous intimal thickening. (Weigert-van Gieson × 181.)

FIG. 23. Human pulmonary artery: eccentric fibrous intimal thickening containing irregularly disposed elastic fibers. (Weigert-van Gieson × 220.)

FIG. 24. Human pulmonary arteries containing organizing blood clot. (Weigert-van Gieson × 80.)

FIG. 25. Small human pulmonary artery partially occluded by fibrin containing carcinoma cells. (Weigert-van Gieson × 220.)

On the basis of the experiment recorded in this paper, these lesions were ascribed to organization mainly of fibrin clot which was seen in all stages in numerous small arteries (figs. 24 and 25). Clots were found both with and without associated carcinomatous emboli.

Even in normal people circulating blood is perhaps not as clot-free as is supposed. The comparatively rapid turnover of platelets, prothrombin and fibrinogen suggests this. Other indirect evidence that blood might be coagulating continuously comes from Sternberger,[49] who claims to have recovered active thrombin from circulating blood by dissociating it from antithrombin. Elevation of recoverable thrombin would be expected to indicate clinical conditions in which fibrin formation is increased. An increase of circulating thrombin is also observed postoperatively and in various thrombotic states and may also be associated with other disorders. Furthermore, the wide variety of conditions in which circulating fibrinolysin can be demonstrated also supports the belief that intravascular coagulation is far commoner than general opinion now holds.[50, 51] The observation of an elevated antifibrinolytic titer in blood after exposure to cold possibly may be correlated with development of intravascular thrombosis observed in frostbite. It is believed a high antifibrinolysin titer represents a response to the presence of excessive fibrinolysin which in turn might indicate thrombosis.[52, 53] Guest and associates[54] have reported increased antifibrinolytic activity in certain clinical states in some of which the possibility of thrombosis existed. Another disease in which numerous blood clots or arteriosclerosis may be found in small arteries is sickle cell anemia. Yater and Hansmann[55] described two cases with hypertrophy and failure of the right heart.

It seems likely that once pathologists become generally aware of how varied thromboembolic arterial lesions really can be, cases otherwise attributable only to primary hypertension will diminish. Study of case reports, however, shows that there are cases which at the present time cannot be ascribed to anything but essential hypertension in the sense that this term applies also to systemic hypertension. However, hypertension in both lesser and greater circulations can remain essential only so long as its causes remain obscure. Further study must thus eventually lead to progressive recognition of symptomatic hypertension in both circuits.

Summary and Conclusions

A long-term experiment has shown that repeated intravenous injections of minute autogenous blood clots into rabbits caused pulmonary arteriosclerosis and cor pulmonale. Intimal incorporation of clot accounted only for eccentric intimal fibrosis sometimes containing new elastic fibers. This is a small fraction of the total lesions caused thromboembolically. All other lesions were circumferential and composed of fibrous tissue by itself (endarteritis obliterans) or of fibrous tissue with new elastic laminae in addition (fibroelastosis); they were ascribed to hypertension and vasospasm. Whether rabbits received repeated injections of fibrin particles or red clot particles, pulmonary arterial lesions were the same. Atherosclerosis was not encountered. Also, medial atrophy was caused by recurrent thromboembolism, not medial hypertrophy. No arterial lesion was specific for animals that developed cor pulmonale.

That this animal experiment has its counterpart in human pathology is supported by case reports, a case of pulmonary lymphangitis carcinomatosa, and evidence that circulating blood is not clot free.

Sumario Español

Un experimento por largo término ha demostrado que repetidas inyecciones de pequeños coágulos autógenos de sangre a conejos causó arteriosclerosis pulmonar y cor pulmonale. La incorporación del coágulo a la íntima explicó solamente fibrosis excéntrica de la íntima algunas veces conteniendo nuevas fibras elásticas. Estas fueron solamente una pequeña fracción de las lesiones totales causadas tromboembolicamente. Todas las otras lesiones fueron circunferenciales y compuestas de tejido fibroso ensí (endarteritis obliterans) o de tejido fibroso con

nuevas láminas elásticas en adición (fibroelastosis); fueron atribuidas a hipertensión y vasoespasmo. Las lesiones arteriales pulmonares fueron iguales no obstante las repetidas inyecciones de partículas de fibrina o partículas de coágulo de sangre. No se encontró ateroesclerosis. También se causó atrofia de la media y no hipertrofia con el tromboembolismo recurrente. No hubo una lesión específica en los animales que desarrollaron cor pulmonale.

Que este experimento animal tiene su duplicado en la patología humana es ostenido por casos informados, un caso de linfangitis pulmonar carcinomatosa y evidencia de que la sangre en circulación no esta libre de coágulos.

Acknowledgments

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Hyperventilation in Postural Hypotension

By JOHN F. BURNUM, M.D., JOHN B. HICKAM, M.D., AND EUGENE A. STEAD, JR., M.D.

In normal subjects hyperventilation causes a drop in arterial blood pressure, apparently because of the direct effect of hypocapnia on the peripheral vessels. In persons with disease of the autonomic nervous system, the drop in blood pressure is much greater because it is not effectively opposed by reflex vasoconstriction. Consequently, hyperventilation caused by anxiety may greatly intensify postural hypotension in such patients and contribute significantly to their disability. A pertinent case is reported.

PATIENTS with postural hypotension from disease of the autonomic nervous system present an easy problem in diagnosis, but a difficult problem in therapy. The purpose of this paper is to point out the unusual response to overbreathing seen in these subjects and to call attention to the fact that prevention of the loss of carbon dioxide may be occasionally of therapeutic importance.

Hyperventilation is a frequent cause of disturbances in consciousness in anxious patients when they are lying down. When these patients stand, increased reflex action from standing, the usual postural fall in cerebral arterial pressure, and anxiety, caused by queer feelings from carbon dioxide loss, combine to produce marked overactivity of the autonomic nervous system and the common faint (reflex vasodyspnea syncope). Unless one faints, large and maintained falls in arterial pressure are not usually seen with emotional overbreathing.

In our experience the disturbances in blood pressure and consciousness produced by standing in patients with disease of the autonomic nervous system are not usually accompanied by hyperventilation. Our attention was called to the adverse effect of carbon dioxide loss on maintaining blood pressure by the following patient:

This 39 year old married white woman (A. M.) was seen at Duke Hospital in August 1952 complaining of attacks of unconsciousness on attempting to stand. She was a known hypertensive for 17 years with minimal signs of blood vessel disease. Thirteen months before entering here she began to lose weight, have a "faraway" feeling and attacks of dyspnea with numbness of the hands and face. In retrospect these seem to have been typical hyperventilation attacks. Six months later, a bilateral lumbodorsal sympathectomy was done at another hospital. Since then she had been incapacitated by inability to stand. On examination the blood pressure was found to be quite variable. On standing it began to fall immediately, and in a short time the radial pulse became imperceptible. As soon as the patient stood, she began to overbreathe obviously, and this became more and more marked until she lost consciousness. It was easy to demonstrate at the bedside that rebreathing into a paper bag caused a considerable lessening of the fall in blood pressure and improved the ability to stand.

The relationships between position, ventilation volume, arterial carbon dioxide pressure and arterial pH are shown in table 1.

Within 82 seconds after tilting, ventilation volume had increased to 31 liters per minute, arterial carbon dioxide tension had fallen to 24 mm. Hg and blood pressure by the auscultating method was unobtainable. Use of a rebreathing mask which prevented carbon dioxide loss allowed a much longer period in the head-up position. In the supine position, breathing of 5 per cent carbon dioxide or breath-holding caused hypertension.

Two additional patients with the syndrome of orthostatic hypotension, fixed pulse, impotency, and impaired sweating, as described in the classic paper of Bradbury and Eggleston, were studied. The etiology was unknown in one and the other had diabetic neuropathy.

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Dr. Burnum is a Life Insurance Medical Research Fellow.

TABLE 1.—*Variations in Arterial Carbon Dioxide Tension and Blood Pressure*

	Ventilation L./min.	Blood Pressure mm. Hg	Arterial Blood	
			pCO_2 mm. Hg	pH
Horizontal	6.2	140/112	37.3	7.37
30° tilt 40 sec.	12.1	80/?	31.9	7.41
30° tilt 82 sec.	31.0	Unobtainable	24.1	7.46
Horizontal		150/100		
Sitting 2 min.		82/76		
Sitting 10 min. with rebreathing mask		112/86		
Horizontal		120/104		
Horizontal after breathing 5% CO_2 for 2 min.		190/140		
Horizontal		162/110		
Horizontal after 45 sec. breath-holding		210/130		

Spontaneous overbreathing was not a problem in either of these patients, but in each patient voluntary forced breathing caused a dramatic fall in arterial pressure (fig. 1). Measurements of the cardiac output by the dye technic showed that the fall in arterial pressure was caused by vasodilation and not by a fall in cardiac output. Forced breathing of 5 per cent carbon dioxide caused no fall.

There was no doubt that in these subjects the postural hypotension resulted from organic disturbances in the sympathetic nervous system. In addition to the findings on physical examination, they all showed the characteristic response of sympathetic paralysis when the Valsalva maneuver was performed.[1] On release of the high intrathoracic pressure, the blood pressure remained at hypotensive levels and did not show the increase in pressure above the resting levels characteristic of a normal autonomic nervous system in the absence of severe heart disease (fig. 2).

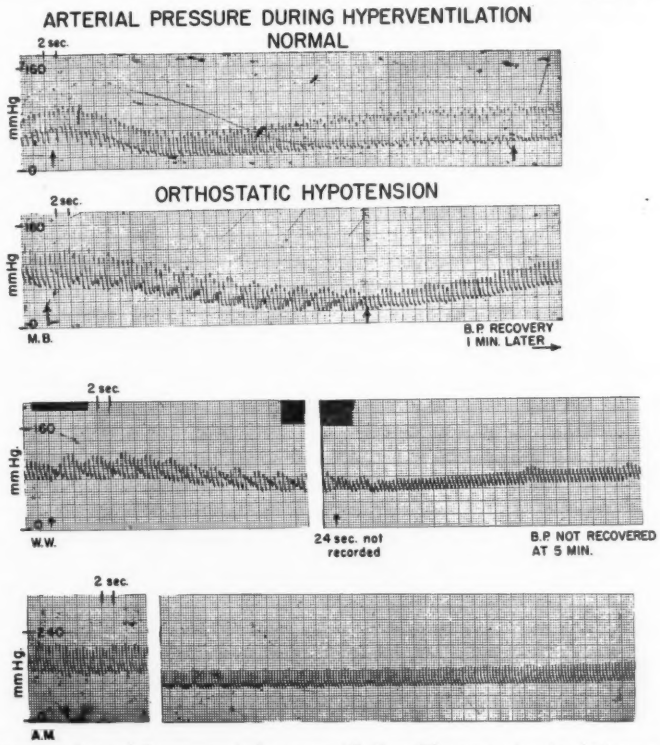

FIG. 1. Response of arterial pressure to hyperventilation. The upper tracing is from a normal subject and the lower three are from the patients described in the text. Hyperventilation begins, in each tracing, at the arrow.

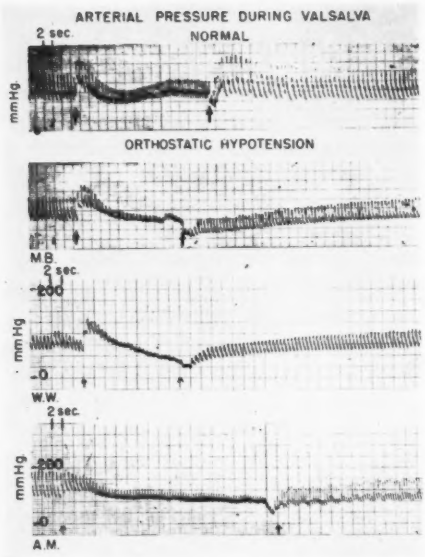

FIG. 2. Response of arterial pressure during Valsalva maneuver. The upper tracing is from a normal subject and the lower three from the patients described in the text. The high intrathoracic pressure was maintained during the period between the arrows.

Laplace[2] noted that in a patient with classic orthostatic hypotension, voluntary hyperventilation while standing precipitated collapse, and that maintenance of arterial carbon dioxide by rebreathing through a piece of tubing prevented hypotension.

Standard textbooks of physiology state that a loss of carbon dioxide from the arterial blood causes (1) vasoconstriction by direct effect on the blood vessels, and (2) vasodilation through effect on the central nervous system; the central effect is dominant and the over-all result is a fall in peripheral resistance. The observation that decreased function of the autonomic nervous system potentiated the vasodilator effect in man led us to doubt that the over-all effect of carbon dioxide deficit on the blood vessels was vasoconstriction. Detailed studies in normal subjects, in patients with most of the sympathetic ganglia removed, and in patients receiving ganglionic blocking agents, showed that the over-all effect of carbon dioxide deficit in the arterial blood was vasodilation, and that this caused a sustained fall in arterial pressure unless it was counteracted by the normal homeostatic neurogenic mechanisms for maintaining constant arterial pressure.[3] Thus, in normal subjects, the fall in peripheral resistance does not cause a large and sustained fall in arterial pressure.

SUMMARY AND CONCLUSIONS

1. A patient with neurogenic postural hypotension is reported who had her postural adaptation made much worse by reflex overbreathing. Attention to the problem of overbreathing simplified the clinical management.

2. Observations on three patients with neurogenic postural hypotension showed that a loss of carbon dioxide by overbreathing produced a striking and sustained hypotension with the patient in the horizontal position.

3. The observation that the greater the defect in the autonomic nervous system, the greater the fall in arterial pressure from overbreathing led to more detailed study of the over-all effects of hypocapnia on the circulation. These results reported in detail elsewhere demonstrate that hypocapnia caused an over-all vasodilation by its direct effect on blood vessels and not by an indirect effect through the nervous system.

SUMARIO ESPAÑOL

1. Una pacienta con hipotensión postural neurogénica se informa en la cual la sobre-ventilación por reflejo acentuó mucho más su adaptación postural. Atención al problema de sobre-ventilación simplificó el manejo clínico.

2. Observaciones en tres pacientes con hipotensión postural neurogénica mostraron que la pérdida de bióxido de carbono debido a la sobre-ventilación produjo una dramática y sostenida hipotensión con el paciente en la posición horizontal.

3. La observación de que mientras mayor sea el defecto en el sistema nervioso autonómico, mayor la caída en presión arterial debido a sobre-ventilación, condujo a un más detallado estudio de los efectos generales de la hipocapnia en la circulación. Estos resultados informados en detalle en otro lugar demuestran que la hipocapnia produce una vasodilatación generalizada por medio de su efecto directo en los vasos sanguíneos y no por un efecto indirecto en el sistema nervioso.

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Effects of an Adrenergic Blocking Agent (Dibenzyline) upon Clinical Manifestations of Arterial Insufficiency in the Extremities

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Adrenergic blocking with Dibenzyline measurably enhances the healing of ischemic ulcers. Eleven cases of obliterative arterial disease and two cases of Raynaud's disease were closely observed and are reported in detail. In six of the individuals suffering from obliterative arterial disease, changes in blood flow were documented by plethysmography. Dibenzyline measurably influenced intermittent claudication only after prolonged administration (three to four months) in four out of eight closely observed patients without ulcers. The results of the physiologic tests suggest that during the early phases of adrenergic blocking the increase in blood flow is mostly in the skin, while in the later phases increase in blood flow through the muscle predominates.

IN the course of testing the effects upon various vascular beds of certain drugs designed to lower arterial pressure, it has been found by a number of workers that several of these drugs had a tendency to increase the rate of blood flow to the extremities and that some of them did so regularly and markedly.[1-7] The strong adrenergic blockers, such as the methonium and Dibenamine derivatives, have a marked effect upon peripheral flow.

It seemed, therefore, worthwhile to observe closely a small number of patients suffering from clinical manifestations of arterial insufficiency and to study the behavior of their extremities in response to adrenergic blocking. The drug which we have so far used most extensively in these studies is Dibenzyline. It was chosen in preference to Dibenamine because it can be used orally. Hexamethonium is a strong adrenergic blocker and has a marked effect upon the blood flow to the extremities, but it is also a cholinergic blocker. Its hypotensive action, furthermore, is so great that its use in long-term experiments on normotensive individuals is impractical. Lately study of another Dibenamine derivative which can be used orally (Ilidar) has been undertaken but is not sufficiently far along to deserve reporting. Its action upon extremity flow seems to be similar to that of Dibenzyline. This report is confined to our experiences with Dibenzyline.

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METHODS AND MATERIAL

Two gross manifestations of arterial insufficiency, gangrenous ulcers and intermittent claudication, were chosen for observation of their response to prolonged adrenergic blocking. So far studies have been concluded in 28 patients, classified in five groups.

1. Raynaud's disease (two cases): Both patients exhibited ulcerations of many fingers of both hands. Both had been subjected to bilateral sympathectomy with transient improvement which had subsided by the time adrenergic blocking was begun.

2. Thromboangiitis obliterans (two cases): These subjects both were suffering from severe pain and extensive ulceration of the extremities. One had lost both lower extremities, two fingers and three distal phalanges of fingers, and the other had lost one toe and distal phalanges of two toes by the time adrenergic blocking was instituted.

3. Obliterative arteriosclerosis with gangrene (nine cases): All of these patients exhibited gangrenous ulcerations on the lower extremities (toes, heels, lower legs). They manifested all the clinical signs of occlusive peripheral arterial disease. Four of them had lost one lower extremity prior to study.

4. Obliterative arteriosclerosis without gangrene (11 cases): These patients presented the clinical picture of intermittent claudication with or without rest pain. They all exhibited signs of arterial insufficiency such as absence of pulsations, coldness and postural color changes.

5. Ulceration attributed to impairment of venous circulation (four cases): None of these patients ex-

h'bited signs of arterial insufficiency. Three of these subjects had leg ulcers attributable to long-standing v:ricosities, refractory to treatment; one had de-v:loped gangrene following trauma complicated by i:fection and thrombophlebitis.

The patients with Raynaud's disease and those w:th obliterative arteriosclerosis without gangrene w:re ambulatory. All of the others were hospital p:tients confined to bed or wheel chair and had been tr:ated in the usual manner, such as postural adjustment, cleanliness, careful dressing, protection by bandages and cradles, use of antibiotics for secondary infections and drainage of abscesses and removal of dead tissue when necessary. This regime remained unchanged throughout the period included in this report. The smoking habits of the patients with obliterative arteriosclerosis were not changed. In the two patients with Buerger's disease, abstinence from tobacco was ordered. In the first case (JM) little cooperation was obtained. It should be noted, however, that there was no apparent correlation between the patient's smoking and the course of her illness. During several months of the acute suppurative pulmonary complication, she did not smoke at all, but was off Dibenzyline. It was then that she had a severe relapse. The second patient (GMS) had stopped smoking five years before treatment with Dibenzyline was started.

Dibenzyline was given in doses ranging from 20 to 480 mg. per day over periods ranging from three weeks to several months. In roughly half of the cases, Dibenzyline was discontinued one or more times. In about half of these it was replaced by placebos while in the other half no medication was given in the intervals.

The criterion used for the establishment of adrenergic blocking was pupillary response, namely, inability of the pupil to dilate in darkness or with 10 per cent Neo-Synephrine.[7] The dose necessary to produce adequate adrenergic blocking varied widely from individual to individual; some tachyphylaxis seemed to develop in the majority of subjects. The physiologic effects of adrenergic blocking were observed in six subjects by measuring blood flow through the upper extremities plethysmographically and by simultaneously recording surface temperatures in repeated experiments. The reflex responses to warming were also measured. Skin flow and muscle flow were estimated according to a recently published procedure.[8] All experiments were done at 20° C. environmental temperature and 55 per cent humidity.

Results

Group 1. Raynaud's Disease

J. C., a woman 44 years of age, had suffered for 13 years from Raynaud's disease with syncopal attacks, pain and small ulcerations on both upper extremities. Right cervical sympathectomy was performed three and one-half years before the present study began, left cervical sympathectomy two and one-half years before. The effect of sympathectomy started to diminish by spring, 1952. By December 1952, there were ulcerations on most of the fingers. The fingers showed bluish discoloration and sclerodactylia.

J. C. was started on Dibenzyline, 60 mg. a day, in April 1952, with healing of ulcers and remission of pain after four weeks. Subsequently Dibenzyline was discontinued and placebo tablets substituted for six weeks, with recurrence of pain and ulcerations in the third week of placebo administration. Dibenzyline therapy was again started at the same dose and again pain subsided and ulcers healed within three weeks. This cycle has since been repeated once more with the use of placebos in the interval and twice more with no medication in the interval; results were always the same. It was noted, however, that in the last experimental period the ulcers started healing only in the fifth week of medication.

L. R., a man 34 years of age, gave a nine-year history of Raynaud's disease. Right and left cervical sympathectomy performed in 1943 and 1944, respectively, were followed by improvement. By 1948 ulcerations on all 10 fingers had reappeared and were extremely painful. At that time a good response was obtained with Roniacol tartrate, which tapered off after about one year.

L. R. ran a very similar course on the same experimental plan as J. C., starting in September 1952, except that he could not tolerate more than 30 mg. of Dibenzyline a day because of disturbances of his sexual function on higher doses. Nevertheless the ulcers healed after several weeks of therapy only to recur three weeks after discontinuing the drug and to heal again on readministration of Dibenzyline.

Both patients were normotensive and developed mild postural hypotension when on Dibenzyline, with an average drop of 10 to 15 mm. Hg both in systolic and diastolic pressures. Capillary microscopy of the nail bed showed similar findings in both cases: giant loops with short or absent arterial limbs were present, while the transition and venous limbs were enormously enlarged (10 to 20 times the

normal average). There was stasis of blood in about two-thirds of the visualized loops and very slow motion of clumped erythrocytes in the remaining third; the blood column showed deep purplish-blue color.

The following changes were observed to occur regularly in the nail-bed capillaries parallel with gross improvement on Dibenzyline: blood flow became visible in about twice as many loops as before, the column moved much faster and the color was brighter, rather reddish than bluish; arterial limbs of about the same length as the venous limbs became visible on most loops; quantitative measurements of change in diameter of transition and venous limbs were not done but they seemed to become narrower.

Group 2. Thromboangiitis Obliterans

J. M., a woman 50 years of age, gave a history of 23 years' duration, starting with heaviness and pain on walking in both legs, ulcer formation on both feet and amputations of toes. She was a heavy smoker, having started at age 12. In 1934, a diagnosis of Raynaud's disease was made and a Leriche operation was performed on left femoral artery in the same year, and on the right femoral artery in 1936. Rest pain has been present in both legs since 1940. In 1943, when a diagnosis of Buerger's disease was made, she stopped smoking "intermittently." (This situation still prevails.) She was admitted to hospital in July 1952 with tenderness, redness and pitting edema of both feet, impending gangrene of left second toe and an ulcerated amputation site on the left fifth toe. A deep gangrenous ulcer about 2.5 cm. in diameter was present at the base of the right great toe on plantar surface and a superficial ulcer on the right heel. Very severe rest pain was present constantly in both lower extremities and somewhat less severe pain in both upper extremities. The patient exhibited all signs of severe arterial insufficiency in both the lower and, to a lesser degree, the upper extremities. The patient had been using codeine and various combinations of analgesics for several years. On admission, heavy sedation was needed. Attempts to substitute placebos for narcotics were unsuccessful. At the time treatment was begun, as much as 350 mg. of Demerol, 100 mg. of codeine, 1.5 Gm. of chloral hydrate and 500 mg. of sodium Amytal in 24 hours was necessary to obtain relief of pain.

The administration of Dibenzyline was begun on Aug. 5, 1952, 60 mg. a day, with rapid increase in dose to 480 mg. a day. By the middle of November 1952, the ulcers had healed on this regimen. At this time the dose was decreased to 360 mg. because of anorexia, dizziness and palpitations. The rest pains, which appeared to be somewhat aggravated during the first six weeks of adrenergic blocking, were markedly diminished by this time and thus permitted the gradual reduction in the amount of narcotic required. At the end of November, the patient developed pneumococcal pneumonia followed by empyema, necessitating surgical drainage. Dibenzyline was discontinued and severe rest pain and ulcerations recurred within a month. A hemorrhagic skin eruption with blebs on both legs led to readministration of Dibenzyline. Starting Jan. 6, 1953, 240 mg. a day were given until discharge on June 4, 1953. By that time all ulcerations had healed, the rest pain had subsided and the use of narcotics had been completely discontinued.

G. M. S., a 47 year old man, gave a history of pain, numbness and coldness of the right, later of the left, foot since 1931 (22 years). Gangrene of the right foot began in 1932. It progressed more rapidly after "sectioning of nerve" in 1933 and necessitated a midthigh amputation of the right leg in 1934. In 1942, injury to the index finger of the left hand, followed by gangrene, necessitated amputation of the finger. Between 1943 and 1946, several amputations of the left lower extremity, the last one being in midthigh, were performed. In 1947, the second and third fingers of the right hand were amputated because of gangrene following injury. He was admitted on Jan. 15, 1953, with gangrene of the right fifth finger and deep gangrenous ulcers on end phalanges of the third and fourth fingers of the left hand. Severe pain and marked inflammatory reaction were present.

Patient was scheduled for amputation when he was started on 60 mg. of Dibenzyline on Feb. 6, 1953. He was treated on the Surgical Service until March, then transferred to the Research Service and treated intensively with 160 mg. of Dibenzyline daily. By June his ulcers were healed. The uppermost tip of the left fifth finger sloughed off, but the finger healed perfectly and appears to be well-supplied with blood. The nail has regrown. His pains started to diminish after about six weeks of adrenergic blocking and have completely subsided.

Group 3. Obliterative Arteriosclerosis with Gangrene

Gangrenous ulcerations which had been under observation for 12 to 80 weeks and which had shown no tendency to heal or had become worse, healed within 4 to 20 weeks after administration of Dibenzyline had been started.

In five of the nine cases reported, the drug was discontinued immediately after healing had taken place. The recurrences were again treated successfully. The daily dose was 60 to 200 mg. (table 1).

TABLE 1.—*Response of Gangrenous Lesions in Nine Cases of Obliterative Arteriosclerosis to Adrenergic Blocking with Dibenzyline*

Name	Age	Sex	Description of Lesions	Duration of Lesions before Adrenergic Blocking	Daily Dose of Dibenzyline	Result	Remarks
G. G.	70	f	Deep round half-dollar size gangrenous ulcer on lateral border of left foot. Severe inflammation	16–20 wks.	100 mg.	Healing within 10 wks.	Pain completely subsided after about 2 wks. of adrenergic blocking
S. K.	60	m	Gangrene of left heel with deep ulceration extending down to tendon, 2 × 2½ cm. Severe inflammation	About 30 wks.	60 mg.	Healing within 8 wks.	Recurrence of ulceration after discontinuation of treatment. Renewed healing after resumption of therapy
J. K.	68	m	Gangrene with 1 × 1 cm. ulcer; hyperkeratotic crust; right external malleolus	56–60 wks.	80–180 mg.	Healing within 12–20 wks.	Severe pain subsided only after 4 mos. Seven months later pain but not ulceration recurred and medication was resumed with success
M. B.	62	m	2 gangrenous ulcers 10 × 5 cm. and 6 × 5 cm. longitudinally on outer aspect of right calf. Extremely severe inflammation	12 wks.	60 mg.	Healing within 4–5 wks.	Treatment discontinued twice (once replaced by placebos) with recurrence within 2 wks. and renewed healing several weeks after reinstitution of therapy
A. M.	62	m	2 gangrenous ulcers 3 × 4 cm. each, one on each heel, extending down to muscle. Gangrene of distal phalanx left 4th toe. Severe inflammation	70–80 wks.	200 mg.	Healing within 16–20 wks.	Severe pain completely subsided after about 3 wks. of adrenergic blocking
W. C.	66	m	Circular dry gangrene 2½ cm. diameter. Surrounding inflammation	8 wks.	60 mg.	Healing within 6–8 wks.	Ulcer recurred 3 wks. after drug was stopped. On resumption of therapy ulcer healed in 4 wks. Patient is diabetic
I. G.	63	m	Gangrene of 2nd and 3rd right toes extending to a semicircular area at the plantar aspect, 6 cm. in diameter with inflammation	20 wks.	60–100 mg.	Arrest of gangrene with mummification within 7 wks.	Treatment was discontinued; gangrene extended; pain and inflammation recurred. Treatment resumed with improvement. Patient is a diabetic
M. O'B.	63	m	Large gangrenous ulcers, of middle and terminal phalanges of 2nd right toe and of end phalanx of right big toe, with inflammation and blistering	15 wks.	60–120 mg.	Healing complete within 8 wks.	Case still under observation. Ulcer has remained healed 6 mos. Patient is diabetic
J. J.	60	f	Deep gangrenous ulcer half-dollar size, plantar surface of left foot	16–20 wks.	120 mg.	Healing within 10 wks.	Case still under observation. Ulcer has remained healed for 7 mos.

Group 4. Obliterative Arteriosclerosis without Gangrene

Objective measurements for potential improvement were employed in eight patients. Since the exercise involved in repeated measurements of claudication time has, in itself, been reported to cause improvement,[9] three additional cases were evaluated subjectively only.

Four patients showed unequivocal objective improvement after 12 weeks or more of treatment with Dibenzyline in doses ranging from 60 to 180 mg. per day. Their ability to walk improved from one-half to two blocks initially to 5 to 10 blocks. Average claudication time measured on the stationary bicycle rose from 50 to 100 seconds initially to 200 to 400 seconds. Subjective improvement was noted in the three patients to whom Dibenzyline was given but who were not subjected to the regular series of objective tests. The remaining four failed to give clear objective evidence of improvement even after treatment for three months or more. Likewise these subjects evidenced little or no subjective improvement.

Group 5. Ulceration Attributed to Impairment of Venous Circulation

This group turned out to represent a sort of control group for the previous groups in whom the arterial blood supply was obviously impaired. There was no real improvement in any of the three cases with ulcers which were thought to be due to impaired venous return on prolonged administration of Dibenzyline in doses from 120 to 360 mg. per day. This observation is of some interest in view of the fact that these ulcers seemed much more superficial than many of the ulcers in the previous groups. In the fourth case (gangrene, following trauma), no benefit was derived from adrenergic blocking continued for four and one-half weeks with the daily administration of 120 mg. of Dibenzyline. It was consequently necessary to amputate the extremity.

Physiologic Documentation

It will be noted (table 2) that after four weeks of adrenergic blocking the average skin temperature of toes had risen significantly, but returned to almost the basic values after three to five months of continued adrenergic blocking; blood flow through the skin showed a similar pattern of response (table 2). In contrast, blood flow through the muscle showed no significant change after four weeks (except for a slightly decreased reflex response to warming), while there was a measurable increase in muscle flow after three to five months.

Discussion

Haimovici[10] was the first to report the clinical use of Dibenzyline in peripheral vascular disease. He noted that during administration of the drug to two cases of Raynaud's disease the

Table 2.—*Effects of Adrenergic Blocking with Dibenzyline on Blood Flow to Skin and Muscle*

Average values and range of 59 experiments on six subjects

	Skin Temp. of Toes (°C)	Max. Reflex Response of Skin Temp. to Warming (°C)	Rate of Blood Flow through Skin (ml./100 ml. tissue min.)	Max. Reflex Response of Blood Flow through Skin to Warming (ml./100 ml. tissue min.)	Rate of Blood Flow through Muscle (ml./100 ml. tissue min.)	Max. Reflex Response of Blood Flow through Muscle to Warming (ml./100 ml. tissue min.)
Base line	22.0 (19.5–23.5)	26.5 (22.5–28.5)	1.6 (0.5–2.9)	15.1 (10.8–24.8)	1.3 (0.4–2.1)	7.9 (6.2–10.4)
After 4 weeks of adrenergic blocking	26.5 (24.0–33.5)	30.5 (28.5–35.0)	2.8 (0.5–4.1)	18.6 (15.6–22.2)	1.0 (0.4–1.4)	4.4 (2.0–7.4)
After 12–20 weeks of adrenergic blocking	22.5 (20.0–25.5)	25.5 (23.0–32.5)	1.8 (0.6–2.0)	14.4 (12.0–15.8)	2.6 (1.6–2.9)	8.0 (4.8–12.5)

typical response to cold could no longer be elicited. Moser and co-workers[11] reported favorable results with Dibenzyline, hexamethonium and Priscoline in vasospastic conditions (causalgia, Raynaud's syndrome); they also treated 10 cases of "traumatic or postoperative arterial insufficiency," 10 cases of thromboangiitis obliterans and eight cases of arteriosclerosis obliterans, with less favorable results. No details are given, and there is no mention of trophic disturbances, ulcer formation or other forms of local tissue necrosis.

The clinical observations presented here have been taken by us to constitute solid evidence that the drug Dibenzyline favorably influenced the healing of ulcerations due to obliterative arterial disease. Physiologic evidence of increased blood flow during the period of administration of the drug was obtained in a small number of these subjects. It seems justified from these observations to conclude that the continuous afflux of adrenergic impulses to the collateral circulation in limbs with grossly impaired primary circulation plays a large role in preventing the healing of ischemic ulcers. Continued blocking of adrenergic impulses to the blood vessels promotes the healing of the ulcers to a degree which has not been observed following sympathectomy or ganglionic blocking. The doses necessary for the prompt healing of small ulcers in the two cases of Raynaud's disease were conspicuously smaller than the amounts which had to be used in cases of obliterative arterial disease.

The effect of adrenergic blocking with Dibenzyline upon intermittent claudication is much less impressive than that upon the healing of ulcers, at least within the first four or six weeks of therapy, probably because within the first few weeks the effect of the drug upon blood flow to the skin is marked, while muscle flow is not influenced (table 2). After 12 to 20 weeks, there is also a definite increase in blood flow through the muscular tissues. Circulation to the skin is primarily affected; only on prolonged administration for many weeks or months is an effect upon circulation through the deeper tissues noted. These findings would seem to indicate that Dibenzyline therapy for this type of case should be maintained for at least 12 weeks. Earlier discontinuance of the drug precludes a clear estimation of its efficacy.

Of considerable interest is the observation that ulcers which were not due to impairment of arterial supply did not respond to adrenergic blocking (three cases thought due to impairment of venous return and one of gangrene following trauma). The lack of improvement in this group strengthens the conclusion that it is the improvement in arterial blood supply as a result of adrenergic blocking and not some other unknown factor which affects the healing of ischemic ulcers.

The observations on the nail-bed capillaries of the two cases of Raynaud's disease are of some interest: the type of capillary loops seen here has been described as a characteristic finding in Raynaud's disease by some workers[12, 13] and in generalized scleroderma by Mueller and co-workers.[14] Acrosclerosis is a quite constant feature in late severe cases of Raynaud's disease[15, 16] and the cases of scleroderma in whom this type of capillary loop was described in the literature gave an early history of "Raynaud's attacks" and later developed trophic disturbances and small ulcers. The changes in the skin capillaries seem quite impressive but their significance remains obscure.

The unwanted side effects of Dibenzyline have been discussed elsewhere.[7] In this study, the following side effects were of major concern: tachycardia, the occasional occurrence of auricular fibrillation, and, in two patients, the development of prolonged dizziness and confusion, alleviated by discontinuation of the drug. These symptoms are sufficiently severe to proscribe treatment in about 1 in 15 individuals. Postural hypotension, headaches, urinary retention, disturbances in ejaculation and gastrointestinal irritation have occurred occasionally, but were never serious enough to exclude a patient from treatment. Disease of the respiratory tract has been pointed out as a contraindication to the use of adrenergic blocking agents[7]; one patient was eliminated from this

study because two attempts at adrenergic blocking were followed by severe asthmatic attacks.

Summary

1. Twenty-four cases with severe impairment of arterial blood flow to the extremities were studied for their response to adrenergic blocking with Dibenzyline.

2. The healing of ischemic ulcerations in two cases of Raynaud's disease, two cases of obliterative thromboangiitis and nine cases of obliterative arteriosclerosis was markedly enhanced; in two cases with gangrene of the toes, necrobiosis was arrested and the gangrene kept dry and mummified.

3. In contrast, ulcerations due to venous stasis and traumatic gangrene in the absence of obvious arterial insufficiency were not influenced in the four cases studied.

4. Objective improvement of intermittent claudication was demonstrated in four out of eight cases of obliterative arteriosclerosis without ulcerations. Subjective improvement was noted in three additional cases. It is stressed that improvement occurred only on prolonged administration of Dibenzyline. These results appeared to be correlated with physiologic findings that increased blood flow through muscle appeared only after 12 or more weeks of medication.

5. The clinical effects of adrenergic blocking are accompanied by increased blood flow to the extremities as demonstrated by plethysmography and measurement of surface temperatures.

Sumario Español

1. Veinte y cuatro casos con severo deterioro de circulación arterial a las extremidades fueron estudiados de acuerdo a su respuesta al bloqueo adrenérgico con "Dibenzyline."

2. La cicatrización de ulceraciones isquémicas en dos casos de la enfermedad de Raynaud's, dos casos de tromboangiítis obliterante y nueve casos de arterioesclerosis obliterante fué marcadamente aligerada; en dos casos con gangrena de los dedos del pié, la necrobiosis fué arrestada, la gangrena se mantuvo seca y momificó.

3. En contraste, ulceraciones debidas a éstasis venoso y gangrena traumática en ausencia de insuficiencia arterial obvia no fueron influenciadas en cuatro casos.

4. Mejoría objetiva de claudicación intermitente fué demonstrada en cuatro de ocho casos de arterioesclerosis obliterante sin ulceraciones. Mejoría subjetiva se notó en tres casos adicionales. Se enfatiza que la mejoría ocurrió solamente después de la prolongada administración de el "Dibenzyline". Estos resultados parecen estar correlacionados con los hallazgos fisiológicos de que el aumento en circulación a través del músculo apareció solamente después de 12 o más semanas de medicamento.

5. Los efectos clínicos de bloqueo adrenérgico son acompañados por un aumento en circulación a las extremidades como se ha demostrado por medio de pletismografía y determinación de temperaturas de superficie.

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Clinical Trial of Ilidar, a New Dibenzazepine Adrenergic Blocking Drug, in the Treatment of Peripheral Vascular Diseases and Miscellaneous Complaints

By HAROLD D. GREEN, M.D., AND HUGH H. DUBOSE, M.D.

Ilidar, a new adrenergic blocking drug, has been administered to 116 patients; follow-up was adequate on 86. The drug was highly effective in patients with predominantly vasospastic disorders and in patients with postphlebetic syndrome, and moderately effective in patients with thromboangiitis and arteriosclerosis. Most patients could tolerate 50 to 75 mg. three to four times a day. Side effects were principally those to be expected from the moderate postural hypotension associated with effective sympathetic blockade, namely, weakness, dizziness, nausea.

THIS paper reports the results of the initial clinical trial of Ilidar, a new adrenergic blocking drug. This drug, originally designated as Ro 2-3248, is one of a new group of dibenzazepine derivatives first described by Wenner.[1] Many of these, the most potent being Ilidar, were shown to be epinephrine antagonists by Randall and Smith.[2] Moore, Richardson and Green[3] found Ilidar to be a prompt, moderately long acting vasodilator when injected intra-arterially in the normally innervated hind limb of dogs. The normal vasoconstrictor response to epinephrine was found to be reversed following intra-arterial Ilidar; this reversal of response persisted in the different experiments for periods of time varying from 1 hour, 17 minutes to 5 hours, 36 minutes. The normal vasoconstrictor response to epinephrine was blocked for a considerably longer period. Tachyphylaxis did not develop with repeated injections; and doses of Ilidar up to 16 mg. per kilogram of body weight, given as intravenous infusions to anesthetized dogs over a half hour period, caused no fatalities in this study.

Ilidar blocks the vasoconstrictor responses to epinephrine, to norepinephrine and to sympathetic nerve impulses in skeletal muscle. In skeletal muscle Ilidar unmasks a latent dilator response to epinephrine, that is, converts the constrictor response to vasodilation. This epinephrine reversal is induced at a lower dose of Ilidar than that required to block the other adrenergic vasoconstrictor responses in skeletal muscle or to block all adrenergic vasoconstrictor responses in skin.[4-8] Ilidar is temporarily stored in fatty tissue and is eliminated by metabolism; only about 5 per cent appears in the urine.[9]

It is well known that the element of vasospasm plays a role in every type of peripheral vascular disease, varying from the tremendous degree present in Raynaud's syndrome to the smaller but definitely demonstrable degree complicating most cases of arteriosclerosis obliterans. Any drug which might be capable of relaxing this vasospasm should be beneficial in these conditions.

Since Ilidar has proved in animal experimentation to be a safe, potent, adrenergic blocking drug capable of relaxing vasospasm due to sympathetic activity, it was felt that a clinical trial of this drug was warranted, with the aim of establishing therapeutically effective

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dose levels, maximum tolerated doses, anticipated side reactions and possible therapeutic potentialities.

Methods

Initial studies with Ilidar* were carried out on 10 healthy medical students. The drug was administered intravenously over a half-hour period in a dose of 1.0 mg per kilogram of body weight. These studies were carried out in a constant temperature room, utilizing copper-constantin thermocouples for skin temperature recordings as previously described.[10]

After these initial studies 73 patients were subjected to temperature studies during which Ilidar was administered intravenously in amounts of 1 mg. per kilogram over the course of one-half to one hour to demonstrate the degree, if any, of vasospastic element present, and thus to predict the probable effectiveness of the drug.

At the time this analysis was begun, 116 patients with various forms of peripheral vascular disorders had been started on oral Ilidar with instructions to increase gradually the dose as tolerated up to four or more such tablets four times a day. The instructions warned the patient not to increase the dose if any side reaction such as dizziness, nausea or vomiting, took place but to drop back to the largest tolerated dose.

During the first part of the study tablets containing 25 or 50 mg. of Ilidar hydrochloride were used; for all of the latter part of the study tablets of 30 or 60 mg. of Ilidar phosphate were used. Both the 25 mg. Ilidar hydrochloride and the 30 mg. Ilidar phosphate tablets contain an equivalent amount of Ilidar base. In order to simplify presentation, we have expressed the results throughout as multiples of the 25 mg. tablets. Ilidar phosphate is less hygroscopic and therefore permits a more stable tablet than the hydrochloride.

Results and Discussion

A. Control Studies on Normal Subjects

All of the 10 normal subjects showed fairly good vasodilation in the upper extremities and moderately good vasodilation in the lower extremities in response to the intravenous infusion of 1 mg. per kilogram of Ilidar when given without associated body warming. None had any significant side effects or any significant fall in arterial blood pressure.

* The Ilidar was kindly supplied by Dr. Elmer Sovringhaus of Hoffmann-LaRoche, Inc., Nutley, N. J. The injectible preparation was a clear, colorless solution with a pH of 6.0, ± 0.1 pH unit, and contained 10 mg. per milliliter of Ilidar phosphate.

B. Results of Intravenous Infusions of Ilidar in Patients

In only 4 of the 73 patients tested in the constant temperature room did the intravenous infusion have to be discontinued because of adverse side reactions. Two of these four patients developed moderate hypotension, one developed nausea and dizziness and the fourth became weak and restless. Fifty-nine of the 73 patients had good to excellent responses, six had no response and the remainder minimal or fair responses. There were several patients in whom obliterative disease was localized to or was more advanced in one extremity. This extremity was likely to show no response while the other extremity showed a good response. Many patients received only a part of the standard 1 mg. per kilogram intravenous dose because they obtained a maximum response prior to completion of the infusion which was discontinued in this event.

C. Categories of Patients Receiving Oral Ilidar

Eighty-six of the original 116 patients were followed closely enough to allow us to attempt to draw certain conclusions including tolerated dose range, therapeutically effective dose range and untoward side effects. These patients were divided into diagnostic categories as shown in table 1.

In order to determine if the age of the patient played any demonstrable role in the tolerance of the drug or its effectiveness, the patients were also divided into arbitrarily selected age groups of 18 to 40 years, 41 to 60 years, and 61 to 79 years. Table 2 divides each of the three arbitrarily selected age groups into three

Table 1.—*Distribution of Patients Treated with Ilidar*

Total started on drug	116
Total followed	86
Breakdown of patients followed	
Arteriosclerotics	29
Sudden arterial occlusion	4
Thromboangiitis obliterans	8
Raynaud's	7
Postphlebitic syndrome	10
Miscellaneous	28

TABLE 2.—*Tabulation of Tolerated Doses and Doses Producing Side Effects in Eighty-six Patients Treated with Ilidar*

Age Group	No. of Patients	A. Patients Experiencing No Side Effects with Ilidar				B. Patients Who Experienced Side Effects with Lowest Dose Given and Stopped Drug					C. Patients Able to Tolerate Average Doses of Ilidar but Who Were Pushed to Tolerance							
		Patient Number	Dose in mg.	Duration Therapy	Total Daily Dose	No. of Patients	Patient Number	Dose in mg.	Duration Therapy	Total Daily Dose	No. of Patients	Patient Number	Tolerated Dose	Total Daily Tolerated Dose	Duration Therapy	Dose Producing Side Reactions	Total Daily Untolerated Dose	Duration Therapy
18–40	14	15M	50 qid	10 days	200	0					10	4R	50 tid	150	1 mo.	75 tid	225	1 day
		11M	75 tid	3 wks.	225							17M	50 tid	150	1 mo.	100 tid	300	2 wks.
		6M	75 tid	1 mo.	225							5R	50 tid	150	4 mo.	100 qid	400	1 mo.
		3M	100 tid	1 mo.	300							28M	50 tid	150	4 mo.	100 tid	200	2 doses
		2SAO	100 qid	6 wks.	400							6TAO	50 qid	200	1 mo.	100 qid	400	1 mo.
		12M	100 qid	2 wks.	400							1TAO	50 qid	200	6 mo.	100 tid	300	3½ mo.
		14M	100 qid	2 wks.	400							10M	75 qid	300	3 wks.	100 qid	200	2 doses
		1R	100 qid	7 wks.	400							4TAO	100 tid	300	1 mo.	150 tid	450	2 mo.
		26M	100 qid	2 mo.	400							5M	100 qid	400	3 mo.	125 qid	500	9 mo.
		27M	100 qid	2 mo.	400							13M	125 qid	500	9 wks.	150 qid	150	1 dose
		16M	125 qid	4 mo.	500													
		1PP	150 tid	2 wks.	450													
		3PP	150 qid	1 mo.	600													
		6PP	200 qid	2 wks.	800													
41–60	21	25M	25 tid	3 wks.	75	6	2PP	50 tid	3 days	150	18	8TAO	25 tid	75	6 wks.	50	50	1 dose
		9PP	50 tid	3 mo.	150		8M	25 qid	2 wks.	200		2TAO	25 qid	100	2 mo.	50 tid	150	2 wks.
		25AS	50 tid	7 mo.	150		11AS	50 bid	1 wk.	100		9M	25 qid	100	3 mo.	50	50	1 dose
		21AS	50 qid	5 mo.	200		6AS	50 qid	1 mo.	200		6R	50 bid	100	3 wks.	75 tid	225	1 mo.
		20M	50 bid	1 mo.	100		9AS	50 qid	2 mo.	200		4AS	50 bid	100	1 mo.	100 tid	300	2 wks.
		7PP	100 tid	8 mo.	300		2AS	25 tid	3 wks.	75		16AS	50 tid	150	6 mo.	50 qid	200	2 mo.
		8PP	100 qid	7 mo.	400							18M	50 tid	150	3 wks.	75	75	1 dose
		2M	150 qid	6 mo.	600							10PP	50 tid	150	3 wks.	100 tid	300	3 wks.
		24M	100 qid	14 mo.	400							7M	50 qid	200	2 wks.	75	75	1 dose
		3R	100 tid	2 mo.	300							23M	50 qid	200	5 wks.	100 qid	400	2 days
		20AS	150 tid	7 mo.	450							26AS	75 tid	225	5 mo.	100 tid	300	1 mo.
		1M	100 qid	1 mo.	400							3TAO	75 tid	225	10 mo.	100	100	1 dose
		4SAO	100 qid	2 mo.	400							15AS	75 qid	300	8 mo.	100	100	1 dose
		19M	100 qid	3½ mo.	400							10AS	100 tid	300	15 mo.	125	125	1 dose
		5PP	100 qid	1 wk.	400							22AS	100 tid	300	1 mo.	125	125	1 dose
		7R	100 qid	3 wks.	400							8AS	100 tid	300	2 mo.	125	125	1 dose
		18AS	150 qid	4 mo.	600							7TAO	100 tid	300	11 mo.	150	150	1 dose
		12AS	150 qid	9 mo.	600							13AS	125 qid	500	10 mo.	150	150	1 dose
		5TAO	200 tid	8 mo.	600													
		2R	150 6x/d	12 mo.	900													
		5PP	200 qid	7 mo.	800													
61–79	10	27AS	50 bid	8 mo.	100	2	23AS	50 qid	2 wks.	200	5	3AS	50 tid	150	1 mo.	100 tid	300	2 mo.
		29AS	50 tid	1 wk.	150		4M	50 bid	2 wks.	100		1AS	75 tid	225	3½ mo.	100 tid	300	10 days
		7AS	50 qid	7 mo.	200							5AS	100 tid	300	4 mo.	125 tid	375	1 day
		21M	50 qid	10 days	200							28AS	125 qid	500	3 mo.	150	150	1 dose
		1SAO	50 qid	5 wks.	200							3SAO	125 qid	500	4 mo.	150 qid	600	1½ mo.
		24AS	75 tid	3 mo.	225													
		17AS	75 qid	1 mo.	300													
		19AS	150 qid	1 mo.	600													
		14AS	150 qid	9 mo.	600													
		22M	100 qid	3 mo.	400													

AS = arteriosclerosis; M = miscellaneous; PP = postphlebitic syndrome; R = Raynaud's; SAO = sudden arterial occlusion; TAO = thromboangiitis obliterans.

categories based on tolerance of the drug: (A) those who did not experience side reactions with the maximum dose taken, (B) those patients who developed side effects with the lowest dose taken, and (C) those who could tolerate the indicated dose but developed side effects when pushed to larger doses. The duration of the medication is also recorded in the tables. This time ranged from 1 week to 15 months. Three of the patients took the drug for more than one year, 17 were on Ilidar continuously for 6 to 12 months and 16 for 3 to 6 months. No evidence of cumulative effect was demonstrated.

D. Hemograms on Patients Receiving Oral Ilidar

All of the patients taking the drug received initial hemograms and were followed carefully from a hematologic aspect with frequent determinations of the hemoglobin, total white blood cell count and differential count. In some of the patients, if the platelet count did not appear adequate on the stained smear, platelet counts were done. In no case was there any evidence of depression of bone marrow activity.

E. Side Reactions in Patients Receiving Minimal Oral Doses of Ilidar

Eight of the 86 patients, on whom we had adequate follow up, experienced side reactions of sufficient severity that the patient discontinued the drug (see table 2B).

(*1*) *Febrile Reactions.* One of these (2AS) had chills, fever and nausea while taking 25 mg. three times a day; the fever began two to three hours after taking a dose of Ilidar. The drug was stopped, but a few days later the patient took one 25 mg. tablet and the fever recurred. After several more days another 25 mg. tablet was taken and again the fever recurred. This reaction was interpreted as drug fever.*

(*2*) *Gastrointestinal Disturbances.* Two patients, (9AS, 11AS) developed severe nausea and vomiting while taking 50 mg. twice a day and four times a day, respectively, which precluded further use of the medication. Since one of these (9AS) had taken the drug for two months the reaction may well have been due to something other than the drug.

(*3*) *Postural Hypotension.* Two patients developed severe postural hypotension (8M, 23AS). In one of these (23AS) this response directly resulted from failure of the patient to obey instructions in that he proceeded to a higher dose of the medication (75 mg.) even though he experienced mild side effects (dizziness) while taking 50 mg. four times a day. This patient continued to have severe postural hypotension for eight or nine days after discontinuing the drug. In the other patient experiencing severe hypotension, it was not established definitely whether he had experienced milder reactions with initial doses and had proceeded against instructions to the next higher dose but it seems likely that he did.

(*4*) *Miscellaneous Symptoms.* Another of the patients (6AS) in this group developed weakness, nausea, vomiting, triple vision, headaches, and syncope after taking doses of 50 mg. four times a day for one month. This patient was also receiving digitalis and quinidine at the same time so it was never clear whether Ilidar was actually playing a role in the production of these symptoms. Since Ilidar in this study has not shown any tendency to an accumulative effect in the dose range used, it seems unlikely that this patient would develop symptoms after being on the drug three or four weeks.

The two remaining patients (2PP, 4M) placed in this group discontinued the drug of their own volition even though the side effects experienced were only mild. Each was taking 50 mg. per dose. One complained of "a washed

* Since this analysis was begun we have started 85 additional patients (total 201 patients) on oral Ilidar. Among this group two patients developed a febrile reaction within two and three hours after an oral dose of Ilidar. Further medication with Ilidar was not given to one. The other consented to take one 25 mg. tablet two more times on different days and had a chill, fever and nausea lasting a few hours after each dose. All three of the patients experiencing febrile reactions had taken the drug for several days to weeks previously without significant side reactions. The patients charts have not been carefully tabulated, but it is our impression that the clinical responses, tolerated doses and side effects were the same in this latter group as in the original 116.

AS = arteriosclerosis; M = miscellaneous; PP = postphlebitic syndrome; R = Raynaud's; SAO = sudden arterial occlusion; TAO = thromboangiitis obliterans.

out feeling" and the other of "slight dizziness" for a short time after each dose.

In summary: only 1 out of 86 patients (2AS) definitely could not tolerate the drug in minimal doses of 25 mg.

F. Side Reactions in Patients Receiving Maximum Tolerated Doses

In the patients purposely pushed to tolerance, the great majority of the symptoms experienced were dizziness, nausea, and weakness with an occasional patient complaining of drowsiness (see table 2C). In most of the instances, nausea could be eliminated by taking the medication after meals rather than before. The original instruction given to each patient requested that the medication be taken before meals, for it was felt that the maximum response as well as maximum detection of side reactions could best be obtained in this manner. The dizziness in most cases would pass off if the patient would lie down for a few minutes. In one or two of the patients the symptom complex of nervousness, weakness, palpitation and sweating suggested hypoglycemic reactions and in one of these cases the symptoms seemed to be alleviated by the ingestion of food.

Diarrhea occurred in three patients. In each case it occurred after the patient had been taking the drug for at least two months, and in each case the diarrhea stopped several days after the drug was discontinued. However paregoric and other antidiarrheal compounds were prescribed by the patients' local physician. In no case could the diarrhea be attributed definitely to Ilidar, but in no instance could it be eliminated as the offending agent.

Two patients had reactivation of previously diagnosed peptic ulcers. A causal relation could not be postulated definitely in these cases.

Several of the patients with weakness and drowsiness seemed to become tolerant of the dose producing these symptoms after several days of the medication and no longer experienced any further unpleasant side reactions. However, these patients were included in table 2C under those experiencing side reactions.

As seen from table 3, many of the symptoms listed occurred only in one patient. In practically no case could these isolated symptoms be attributed definitely to Ilidar. The majority of the symptoms occurred in the miscellaneous group of patients, many of whom had multiple complaints prior to medication and were difficult to evaluate from this standpoint.

In only one instance did the medication seem to aggravate the pre-existing symptoms for which the drug was given. This was in an elderly man with arteriosclerosis obliterans who complained of a severe intensification of the

TABLE 3.—*Type and Frequency of Side Effects in 86 Patients (All Ages)*

	Symptoms with Lowest Dose			Symptoms when Dose Pushed		
Age Group	18–40	41–60	60–79	18–40	41–60	61–79
No. of Patients	None	6	1	10	19	4
Symptom						
Dizziness*	0	0	1	4	10	4
Nausea†	0	3	0	2	8	1
Weakness	0	3	0	1	5	0
Syncope‡	0	2	1	0	1	0
Drowsiness	0	1	0	3	0	0
Diarrhea§	0	0	0	0	1	2
Burning skin	0	0	0	1	2	0
Vomiting	0	3	0	0	0	0
Headache	0	1	0	0	0	1
Nervousness	0	0	0	1	1	0
Nasal stuffiness	0	0	0	1	1	0
Triple vision	0	1	0	0	0	0
Blurred vision	0	0	0	1	0	1
Trembly	0	1	0	0	1	0
Drug fever	0	1	0	0	0	0
Sweating	0	0	0	0	1	0
Tinnitus	0	0	0	0	1	0
Precordial pain	0	0	0	0	1	0
Abdominal cramps	0	0	0	0	0	1
Deafness	0	0	0	0	1	0
Irritable	0	0	0	1	0	0
Hair standing on end	0	0	0	0	1	0
Palpitation	0	0	0	0	1	0
Pruritis (? hives)	0	0	0	1	0	0
Spontaneous voiding	0	0	0	0	0	1
Hot flashes	0	0	0	0	1	0

* Dizziness, relieved by lying down in majority of cases.

† Nausea occurred only if drug taken on empty stomach in majority of cases.

‡ Syncope associated on two occasions with severe postural hypotension.

§ In every case in which diarrhea occurred, it was only after patient had been on continuous therapy for at least two months, so etiology always in doubt.

burning sensation in his legs while on Ilidar. He was relieved by stopping the drug.

c. Summary of Tolerated Doses.

During most of the study 25 mg. tablets were available. The analysis of doses were complicated, however, by the fact that during part of the study the smallest available tablet was 50 mg. Of the total of 86 patients, 41 voluntarily increased the dose progressively to tolerance, and 45 did not increase the dose to the point where they experienced side effects.

(*1*) *Initial Test Doses.* All patients took an initial single test dose of 25 or 50 mg. without side effects.

(*2*) *Repeated Doses of 25 mg. (75 to 100 mg. per Day).* Two of the 86 patients (8M, 2AS) in this series developed hypotension or drug fever on repeated doses of 25 mg., and discontinued the drug. Two patients (8TAO, 9M) tried single doses and one repeated doses of 50 mg. but developed side effects. They dropped back to 25 mg. which they were able to take without symptoms. One patient (25M) did not try larger doses. Six patients who started initially on repeated doses of 50 mg. (the smallest tablet then available) developed side effects and stopped taking the drug. They are included in paragraph (3) below, but since they did not try 25 mg. they are not included in the analysis of the 25 mg. dose. The remaining patients tolerated well this and larger doses. Thus, 97 per cent (78 out of 80) tolerated repeated doses of 25 mg. or more without side effects; and 2 per cent (2 of 86) could not tolerate repeated 25 mg. doses.

(*3*) *Repeated Doses of 50 mg. (150 to 200 mg. per Day).* Of the 86 patients 83 tried one or more 50 mg. doses. Nine of the 83 experienced dizziness, nausea, weakness, vomiting, hypotension, burning of the skin or cutis anserina; six of the nine stopped the drug (2PP, 11AS, 6AS, 9AS, 23AS, 4M), three dropped back to and continued satisfactorily with 25 mg. doses (8TAO, 9M, 2TAO). One patient (16AS) tolerated 50 mg. three times a day, but experienced precordial pain, weakness, and dizziness whenever he tried to increase the dose to 50 mg. four times a day. Ten patients did not attempt to increase the dose. Four patients (4R, 6R, 18M, 7M) developed side effects at 75 mg. doses and dropped back to 50 mg. doses and nine patients (17M, 5R, 28M, 6TAO, 1TAO, 4AS, 10PP, 23M, 3AS) tried 100 mg. and dropped back to 50 mg. doses which they were able to tolerate without side effects. The remaining 50 tolerated larger doses. Thus 86 per cent (74 out of 86) could tolerate repeated doses of 50 mg. or larger and 13 per cent (11 of 86) experienced side effects with 50 mg. or less three to four times a day.

(*4*) *Repeated Doses of 75 mg. (225 to 300 mg. per Day).* Of the 63 patients who tried doses larger than 50 mg., 54 tried one or more doses of 75 mg. and nine skipped the 75 mg. dose and tried 100 mg. doses, since 25 mg. tablets were not available to them. Of the 54 who tried one or more 75 mg. doses, four experienced orthostatic dizziness, blacking out and reduced hearing and weakness and trembling relieved by eating (4R, 6R, 18M, 7M). All four dropped back to and continued satisfactorily at repeated doses of 50 mg. Four (11M, 6M, 17AS, 24AS) of the eight who did not experience side effects at 75 mg. per dose, did not increase the dose further; five of the 9 patients (10M, 26AS, 3TAO, 15AS, 1AS) tried repeated doses of 100 mg. and dropped back to 75 mg. because of side effects at the larger doses. Forty-one patients tolerated repeated doses larger than 75 mg. Thus 58 per cent (50 of 86) could tolerate doses of 75 mg. or more without side effects and 17 per cent (15 of 86) experienced side effects with doses of 75 mg. or less three to four times a day.

(*5*) *Repeated Doses of 100 mg. (300 to 400 mg. per Day).* Of the 86 patients, 55 tried one or more doses of 100 mg. Fourteen of these experienced dizziness, nausea, weakness, nasal stuffiness, diarrhea, headache, urticaria, pruritus, hot flashes, or drowsiness or were irritable and nervous; nine of these (17M, 5R, 28M, 6TAO, 1TAO, 4AS, 10PP, 23M, 3AS) dropped back to 50 mg. doses, and five (10M, 26AS, 3TAO, 15AS, 1AS) dropped back to 75 mg. doses which they could tolerate. Seventeen patients did not try to increase the dose above 100 mg. Five (5M, 10AS, 22AS, 8AS, 5AS) tried to increase the dose to 125 mg. and two (4TAO, 7TAO) tried to increase the dose to

TABLE 4.—*Relationship of Age to Tolerated Dose in Milligrams*

		Age Groups		
		18–40	41–60	61–79
Doses that did not produce side effects	No. of patients	24	39	15
Single dose	Mean	93	89	85
	Standard deviation	39	46	38
	Range	50–200	25–200	50–125
Total daily dose	Mean	342	318	310
	Standard deviation	162	202	168
	Range	150–800	75–900	100–600
Single dose producing side effects	No. of patients	10	24	7
	Mean	110	81	104
	Standard deviation	24	37	42
	Range	75–150	25–150	50–150

150 mg.; but, because of side effects, these seven patients dropped back to repeated doses of 100 mg. Seventeen patients tolerated larger doses. Thus 48 per cent (41 of 86) could tolerate repeated doses of 100 mg. or larger and 34 per cent (29 of 86) experienced side effects at doses of 100 mg. or less three to four times a day.

(*6*) *Repeated Doses of 125 mg. (375 to 500 mg. per Day)*. Twenty-two patients tried repeated doses of 125 mg.; five of these (5M, 10AS, 22AS, 8AS, 5AS) experienced dizziness, nausea on an empty stomach, loss of energy, and nervousness, and dropped back to 100 mg. which they took without side effects. One (16M) did not increase the dose further, four (13M, 13AS, 28AS, 3SAO) tried doses of 150 mg. but experienced side effects so dropped back to 125 mg., and 12 tolerated larger doses. Thus 20 per cent (17 of 86) could tolerate repeated doses of 125 mg. or larger, and 40 per cent (34 of 86) experienced side effects at repeated doses of 125 mg. or less, three to four times a day.

(*7*) *Repeated Doses of 150 mg. (450 to 600 mg. per Day)*. Eighteen patients tried repeated doses of 150 mg. Six of these experienced dizziness, weakness, sluggishness, palpitation, sweating, tinnitus, blurred vision and colic. Four of them (13M, 13AS, 28AS, 3SAO) dropped back to 125 mg. and two (4TAO, 7TAO) dropped back to 100 mg. doses which they took without side effects. Nine patients did not try to increase the dose further; one of these (2R), however, took the 150 mg. dose six times a day for a daily dose of 900 mg. Three patients tolerated larger doses. Thus 14 per cent (12 of 86) could tolerate repeated doses of 150 mg. or larger, and 47 per cent (40 of 86) experienced side effects with repeated doses of 150 mg. or less.

(*8*) *Repeated Doses of 200 mg. (600 to 800 mg. per Day)*. Three patients (5TAO, 6PP, 5PP) (3 per cent) took repeated doses of 200 mg. without side effects. From group (7) above, one patient (2R), took 150 mg. six times a day and six more (3PP, 2M, 18AS, 12AS, 19AS, 14AS) took 150 mg. four times a day. Thus 12 per cent (10 of 86) could tolerate total daily doses of 600 mg. or larger.

(*9*) *Relationship of Age to Tolerance*. It is apparent from table 4 that the average daily tolerated dose is in the range of 300 mg. divided into three or four doses. As shown in tables 2 and 4, there is no significant difference in the tolerance of the drug in the three age groups nor is there any significant difference in the doses producing side effects in the three groups.

H. Therapeutic Dose Range

The total daily dose in patients benefitted from the drug ranged from 50 mg. to 900 mg. per day. In general, improvement seemed to increase in proportion to the total dosage but there was a good bit of individual variation in this regard. On the basis of these studies, it is

not felt that any great benefits are derived in exceeding a dose corresponding to repeated doses of 75 to 100 mg. (total daily doses of 225 to 400 mg.).

1. Therapeutic Impressions

The chief interest in this initial clinical trial with Ilidar was to investigate and establish its tolerated dose, side reactions and untoward complications. In regard to therapeutic response no controlled series was run and in only a few patients was Ilidar used alone. Therefore only an impression as to the therapeutic effectiveness of Ilidar can be gained from the patients studied thus far. Simultaneous therapy of one kind or another was used in most patients. Many of the arteriosclerotics were receiving low fat diet, lipotropic agents, B_{12}, thiamine, sedation, analgesia and the usual instructions to walk slower and discontinue tobacco. Many of the patients with edema were given elastic stockings and those with stasis dermatitis and ulcerations received local skin therapy. Many were put on weight reduction diets, modified activity with rest periods of leg elevation, and similar regimens, all tending to relieve symptoms. Therefore, except for several patients with Raynaud's syndrome and one or two in each of the other groups as mentioned below, any beneficial results cannot be attributed to any one therapeutic agent. The majority of the patients included in the miscellaneous group received *only* Ilidar.

(*1*) *Arteriosclerosis Obliterans.* Of the 29 patients classified as having arteriosclerosis obliterans, about 10 or 34 per cent obtained some symptomatic benefit while using Ilidar. The complaint of intermittent claudication was uniformly unrelieved. The symptoms of aching, burning, coldness, night cramps and numbness seemed to respond best to Ilidar. There was no uniform evidence of objective improvement in these patients as measured by the treadmill tolerance test. Five of those showing no benefit were patients who experienced side effects with minimal doses of 25 mg. to 50 mg.

(*2*) *Sudden Arterial Occlusion.* Three of the group of four patients having classical signs and symptoms of sudden arterial occlusion were 56 years of age or older and the occlusions were thought to be due to thrombosis secondary to arteriosclerosis. The fourth was a 29 year old male with sudden occlusion of the left popliteal artery with no apparent cause for thrombosis or embolism. Two of these patients obtained partial relief of symptoms which included numbness, pain and coldness, but exercise capacity improved in only one who gradually obtained complete relief from intermittent claudication over a two month period while talking Ilidar. None of these patients were seen in the first few days following their apparent sudden arterial occlusion. Amputation was not necessary in any of these patients.

(*3*) *Thromboangiitis Obliterans.* Five of a group of eight patients with thromboangiitis obliterans experienced subjective improvement while taking Ilidar. The symptoms of coldness, aching and burning responded most often and most satisfactorily. Two patients observed a moderate improvement in claudication. These two patients had good responses to the intravenous test. This improvement continued in one even though the drug was stopped. The other noted a return of all symptoms during a trial period off the drug with recurrence of beneficial effect after restarting the drug. In the cases of thromboangiitis obliterans, there seemed to be no correlation between the dose and the benefit obtained.

(*4*) *Raynaud's Syndrome.* Seven patients with vasospastic disease (Raynaud's syndrome) were treated with Ilidar. Five of these or about 70 per cent obtained beneficial results. Two of these experienced rapid, complete relief of symptoms including cold, painful, blanched and swollen fingers. One of these patients who obtained complete relief had been troubled for four years with severe symptoms that apparently followed an electrical burn. Two patients received no benefit whatsoever. It is interesting that both of these patients obtained excellent responses to the intravenous test but could tolerate only the relatively small oral doses of 50 mg. three times a day. The five patients who did benefit were able to tolerate larger doses than the two who did not respond.

(*5*) *Postphlebitic Syndrome.* Eighty per cent of a group of 10 patients diagnosed as postphlebitic syndrome showed improvement on Ilidar.

These patients had edema, tender red areas along the course of veins, stasis dermatitis and superficial ulcerations, tightness in the calves and one had intermittent claudication. In those benefitted there was moderate to complete relief of symptoms including claudication in the one instance; and objectively there was definite reduction in stasis edema, improvement of the associated dermititis and healing of the stasis ulcers in three cases. One of the two that failed to benefit was unable to tolerate the drug and discontinued its use after three days on small doses.

(*6*) *Miscellaneous.* A group of 28 patients were classified as miscellaneous. Ten of these seemed to benefit symptomatically from Ilidar. Five of these had evidence from temperature studies of increased vasospasm in the lower extremities and occasionally the upper extremities. These patients complained of coldness of the extremities, aching in calves and burning of the feet. All of the symptoms were aggravated during cold weather and several of this group found they needed to take Ilidar only during the colder months as they remained asymptomatic without medication during the summer. At least one of these patients is starting his second winter since being started on Ilidar and after being free of symptoms all summer, is finding it necessary to take Ilidar again and is obtaining marked symptomatic relief.

Two patients with paravertebral muscle spasm and pain associated with osteoarthritis of the spine reported they gained complete relief of symptoms after starting Ilidar. The benefit continued after the drug was discontinued. Two or three patients diagnosed as causalgia also obtained symptomatic relief.

The most dramatic response in the entire series was that of a 32 year old male diagnosed as acrosclerosis. He had noted stiff, painful fingers for the past nine months and was unable to close his hands when first seen. After two weeks of Ilidar, during which time the only other therapy consisted in the avoidance of tobacco, he showed remarkable improvement and was able to play golf for the first time in seven months.

Summary and Conclusions

This study describes our clinical experiences with Ilidar, a new adrenergic blocking agent.

An initial study was carried out using 10 normal medical students who received intravenous infusions of Ilidar while in a constant temperature room where continuous skin temperatures were recorded. In all 10 satisfactory relaxation of cold induced vasoconstriction was obtained, and no significant side effects were noted.

Seventy-three patients were subjected to a similar intravenous test. A marked vasodilating effect was noted in all but 14 who had moderate to advanced obliterative arterial disease. Sixty-nine of the 73 tolerated the drug without significant side effects.

One hundred sixteen patients, most of whom had some form of peripheral vascular disorder involving a vasospastic component, were treated with oral Ilidar. Follow up was adequate on 86 of these patients.

In this study the Ilidar was well tolerated, in therapeutically effective oral doses, by 74 of the 86 patients. Only 1 of 86 individuals could not tolerate the drug in any amount. Drug fever and severe nausea and vomiting were the manifestations of these apparent idiosyncrasies.

In 33 of the patients the dose was increased progressively until side effects were experienced. Those most commonly noted were dizziness, nausea, weakness, syncope and drowsiness. Eighty-six per cent of the patients tolerated 150 to 200 mg. a day; 58 per cent tolerated 225 to 300 mg. a day, and 34 per cent tolerated 300 to 400 mg. a day given in three or four divided doses a day. From these observations it is concluded that, for the majority of patients the oral medication should be in the range of 50 to 75 mg. three or four times daily, though in a fair number of patients dosage can be pushed to higher levels if necessary.

No apparent long-time cumulative effect of the medication and no bone marrow depression were noted in the 36 patients who took the drug continously from 3 to 15 months.

The mildness and infrequency of the side reactions make Ilidar one of the most pleasant drugs in its class to use. However, the mildness of the reactions may constitute one of its

greatest hazards in that it may allow an occasional patient to reach a dosage which results in a high degree of sympathetic blockade and possibly in serious hypotensive episodes without the preliminary warning of less serious toxic manifestations. Careful patient instruction should, however, virtually eliminate this possibility.

The drug proved highly effective in patients with predominantly vasospastic disorders as manifest by coldness, blanching and aching of the extremities, especially when aggravated by cold weather. Healing of superficial ulceration was noted in several of this group. Relief was experienced by several patients with vague symptoms suggestive of myalgia. Significant benefit was noted in patients with the postphlebitic syndrome when used in conjunction with supportive therapy. Subjective improvement was noted in five of eight patients with thromboangiitis obliterans and in 34 per cent of 29 patients classified as having arteriosclerosis obliterans, and in three of four patients who had experienced sudden arterial occlusion.

Sumario Español

"Ilidar," un nuevo agente bloqueador adrenérgico, ha sido administrado a 116 pacientes; observación continua fué adecuada en 86. La droga fué altamente eficaz en pacientes con desordenes predominantemente vasoespásticos y en pacientes con síndromes postflebíticos y moderadamente efectiva en pacientes con tromboangiítis y arterioesclerosis. La mayor parte de los pacientes pudo tolerar de 50 a 75 mg. tres o cuatro veces al día. Los efectos no deseables fueron principalmente aquellos que se esperaban de la moderada hipotensión postural asociada con un bloqueo simpático efectivo, o sean, debilidad, mareos y nausea.

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Analysis of the Electrocardiograms Obtained from 1000 Young Healthy Aviators

Ten Year Follow-up

By Lt. John M. Packard, MC, USN, John S. Graettinger, M.D., and Capt. Ashton Graybiel, MC, USN

Ninety-six per cent of the original subjects were traced after a period of 10 to 12 years; 202 were dead, and data obtained on re-examination were complete for 639. Except in one case of myocardial infarction, subjects with "borderline" or frank electrocardiographic abnormalities showed no symptoms of the development of heart disease. It is argued that the borderline abnormalities, considered as a group, must have little pathologic significance; otherwise, out of the relatively large number of subjects in this group, some would have exhibited symptoms. Although heart disease did not develop in any of the subjects with frank electrocardiographic abnormalities, such as bundle-branch block, the same argument does not hold with equal force because of the small number of cases in that group.

AN ANALYSIS of the electrocardiograms obtained from 1000 young healthy aviators was reported 10 years ago from this laboratory.[1] The results of the analysis were of interest chiefly because some of the findings fell outside the range generally considered to be normal. At that time it was impossible to decide whether the normal range should be extended or whether these findings were to be attributed to unrecognized heart disease. Since these electrocardiographic abnormalities occurred in healthy persons, they were tentatively classified as "borderline," and two lines of inquiry were followed in an effort to assess their significance.

The first approach consisted in determining if the borderline abnormalities observed in the pilot group were to be found in the electrocardiograms obtained from younger subjects. Accordingly, a cardiovascular survey was carried out on 2600 healthy school children in whom degenerative heart disease was extremely unlikely.[2] Not only were the same borderline variations discovered, but they appeared more frequently than in the pilot group. The exception to this generalization was a single instance of left bundle branch block in one of the pilots. The second approach, which forms the basis of this report, was a follow-up study of the original group of pilots after an interval of at least 10 years.

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Subjects and Procedure

One thousand pilots and flight students served as subjects for the first electrocardiographic study which was carried out from July 1940 to March 1942.* Nine hundred and fifteen were naval aviators or flight students, and the remainder were advanced student aviators in one of the government sponsored training programs. They were all men whose ages ranged from 20 to 30 years with a mean of 23.7 years. They had been selected for flight training only after meeting the most exacting physical requirements and, in addition, each subject received a careful physical examination at the time the studies were made. None had signs, symptoms, or a history of heart disease. The electrocardiograms (leads I, II, III, CF_4, CR_4) were recorded using an amplifier type of electrocardiograph (Sanborn Cardiette). In all but a few instances the subjects were under basal conditions at the time the record was obtained.

The subjects have recently been traced through use of Navy, Marine Corps, Veterans Administration, and Civil Aeronautics Administration files and through information received from colleges, families, former employers, and other subjects.

* In the remainder of the paper this will be referred to as the "first" or the "1940" examination.

During a three year period starting in 1950, it was possible to trace 96 per cent of the subjects (table 1).

Two hundred and two men (20 per cent) were known to be dead: Trauma was the principal cause of death (193 fatalities) with aviation accidents and aerial combat accounting for 175 of the fatalities; disease caused only seven deaths; in two cases the cause of death has not been learned. Heart disease caused the death of but one man who died in 1952 at 32 years of age of a second myocardial infarction (fig. 1). Analysis of the 1940 electrocardiograms of the deceased subjects showed that no statistically significant increase in mortality occurred in association with any electrocardiographic alteration.

Seven hundred and three subjects (88 per cent of the survivors) were re-examined after 10 to 12 years.* The majority were examined by two of the authors (JMP and JSG) utilizing a mobile laboratory containing an electrocardiograph and a portable x-ray unit which made it possible to conduct the examinations at the subjects' homes or places of business. Many subjects who lived in localities remote from the itinerary of the mobile unit, including those overseas, were examined for us by medical officers in nearby Armed Forces or Veterans Administration installations or by private physicians. Our examination was comprehensive; it included measurements of the blood pressure and pulse rate in the supine and standing positions, a teleroentgenogram of the chest, and an electrocardiogram. In the case of a number of subjects with whom personal contact could not be made, routine military or Civil Aeronautics Administration physical examinations for 1951 and 1952 were reviewed. These examinations were less complete and did not include an electrocardiogram. Sanborn Cardiettes were used by us but many different makes of electrocardiographs were utilized by the other examiners. The tracings in all but a few cases included the augmented unipolar and bipolar limb leads and the usual six unipolar precordial leads.

The rate, rhythm, and the durations of P-R, QRS, and Q-T were measured in the usual manner. Since a change in the relationship of the electrical field of the heart to the recording electrodes alters the amplitude and configuration of electrocardiographic leads and since differences in electrocardiographic technic also cause changes in electrocardiographic tracings, lead by lead comparisons of the amplitudes of the deflections were not made. Estimations of the positions of the mean electrical axes of QRS and T in the frontal plane were made in both sets of electrocardiograms by the technic of Grant and Estes.[3] In addition, changes in the amplitude or configuration of the deflections which could not be attributed to a shift in the electrical field of the heart were noted. All measurements were carried out by two of the authors (JMP and JSG) and were coded on International Business Machine punch cards.

* Referred to as the "second" or the "1950" examination hereafter.

TABLE 1.—*Ten Year Follow-up of 1000 Aviators*

Total followed		960	96%
Dead	202		
Re-examined	703		
History only	55		
Lost to follow-up		40	4%

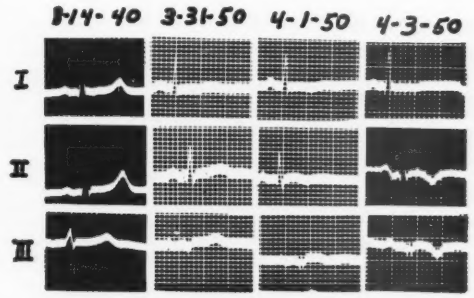

FIG. 1. Serial electrocardiograms from the only aviator subject dying of heart disease. The only predisposing physical factor was an abnormally high serum cholesterol (340 mg. per 100 cc.) found two years before death.

RESULTS

Almost all of the 703 men re-examined were in good health, and only four had objective evidence of heart disease. Two had hypertensive heart disease, and one had an enlarged heart following pulmonary embolization; the electrocardiograms of these men remained normal. The fourth man had survived a posterior myocardial infarction, and his electrocardiogram showed the typical Q_3T_3 pattern. In addition, eight men had enlargement of the heart by x-ray films without other evidence of heart disease, and 12 had blood pressures greater than 145/95 mm. Hg. The electrocardiograms of these 20 men were normal.

The examinations of 645 of these men included electrocardiograms which were suitable for analysis. Six abnormal records were not included in the statistical analysis but will be discussed in the appropriate sections. These six records include two instances of the Wolff-Parkinson-White syndrome, two records showing right bundle-branch block, one showing

TABLE 2.—*Distribution of Heart Rates in 1940 and 1950. Examinations of 639 Subjects*

1950 Rate	1940 Rate								Total
	30–39	40–49	50–59	60–69	70–79	80–89	90–99	100–109	
30–39									0
40–49		1	2						3
50–59		7	17	9	3	1			37
60–69		13	55	52	22	4		1	147
70–79	1	11	86	82	44	20	4		248
80–89		8	26	46	27	6	3		116
90–99			14	29	12	9	2		66
100–109			4	6	2	1	2		15
110–119			1	4		1			6
120–129									0
130–139						1			1
Total	1	40	205	228	110	43	11	1	639

1940 Mean heart rate 63.5; standard deviation 10.6; ±2 SD = 42.3–84.7.

1950 Mean heart rate 74.6; standard deviation 11.8; ±2 SD = 51.0–98.2.

left bundle-branch block, and one characteristic of myocardial infarction. The following statistical analysis is therefore based on the measurements of two electrocardiograms obtained 10 or more years apart from each of 639 healthy men.

Heart Rate and Rhythm

Because the electrocardiograms were obtained with the subjects under basal conditions during the first examination but not during the second, it was not surprising that the mean heart rate had increased from 63.5 to 74.6 beats per minute. Table 2 shows the 1940 and the 1950 rate for each subject and gives the distribution, the mean, and the standard deviation of the heart rates in the two examinations. In addition, a range is derived by adding and subtracting two standard deviations from the mean heart rate. Statistically, 96 per cent of normal values will fall within this range, and the greater a given value deviates from these limits, the less probable is it that the value is normal. Accordingly, our data indicate that 96 per cent of healthy males 20 to 30 years of age have basal heart rates between 40 and 85, while 96 per cent of men 30 to 40 years of age who are not under basal conditions have heart rates between 50 and 100.

Sinus Bradycardia. At the time of the initial examination heart rates below 60 were common (39 per cent of the subjects) whereas on the second examination only 6 per cent of the subjects showed sinus bradycardia (table 2). One subject who had had the extraordinarily slow heart rate of 38 was found to have a rate of 75 at the second examination (fig. 2*A*). He had remained in good health, and the configuration of his electrocardiogram had not been significantly altered.

Sinus Tachycardia. The number of men with heart rates greater than 100 increased from 1 (0.2 per cent) to 22 (3 per cent). In most of these subjects the rapid rate was ascribed to tension at the time of the examination, but the subject with the fastest rate (135) presented signs and symptoms suggestive of thyrotoxicosis. Depression of the RS-T segment and T waves was observed in the electrocardiograms of certain subjects with marked increases in heart rates (fig. 2*B*). Marked change in rate was not regularly accompanied by ST-T change, however, as can be seen by comparison of the first and second tracings in figure 2*A*.

Variations in the Location of the Pacemaker. The tracings of 11 of the re-examined men showed wandering of the pacemaker in and about the sinoatrial (S-A) node in 1940; it was absent in all but one of these tracings in 1950. In one instance it appeared during the second examination but not during the first. There were two instances of S-A block with nodal escape on the first examination; both subjects remained in good health and had normal electrocardiograms at the time of the second examination. Another man with atrioventricular nodal rhythm in 1940 was still in good health and active as a pilot in 1950, but we have not yet been able to obtain a second electrocardiogram. The S-A node was the pacemaker in the 1950 electrocardiograms of all but one subject, a healthy 33 year old military aviator with previously normal rhythm who was found to have asymptomatic auricular fibrillation. No cause for the arrhythmia was demonstrated, and his rhythm reverted to normal following the administration of quinidine.

Short P-R Interval and Wide QRS Waves.

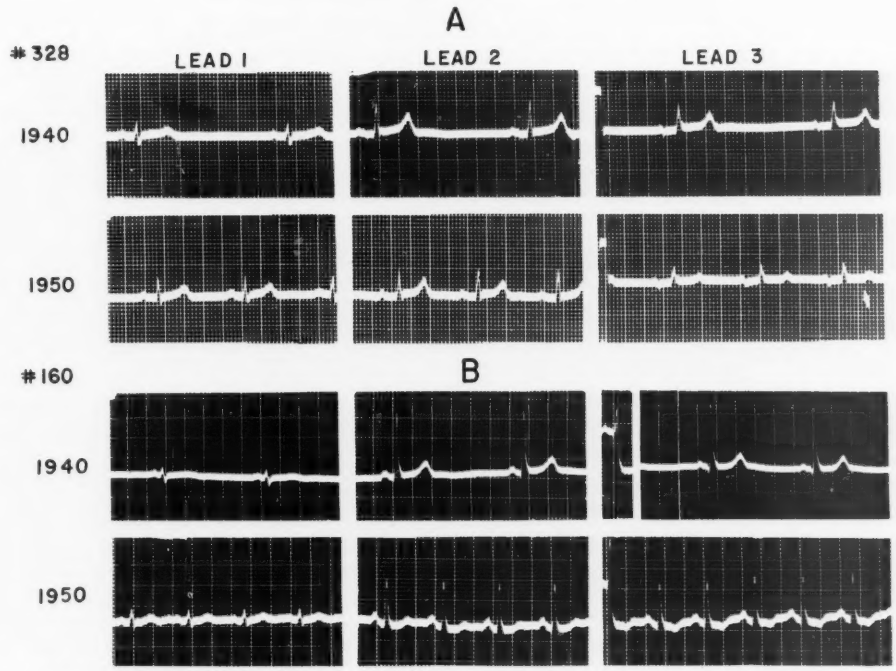

FIG. 2A. The 1940 and 1950 electrocardiograms of a healthy aviator whose heart rate increased from 38 to 75. Note the similarity in the configurations of the P, QRS, and T waves, and the constancy of the P-R interval. (*B*) The 1940 and 1950 electrocardiograms of a healthy aviator which demonstrate changes in P wave, decreased amplitude of QRS, depression of the RS-T segment, and a shift in T axis from +85 to −10 degrees with an increase in rate from 50 to 110.

In the first study there were two subjects whose electrocardiograms showed the syndrome first described by Wolff, Parkinson, and White.[4] One was killed in an aircraft accident; it is not known if he had experienced attacks of paroxysmal tachycardia. The other man remained in good health and without symptoms; his 1950 electrocardiogram was unchanged. A third subject, whose electrocardiogram had been normal in 1940, had a tracing in 1950 which showed a series of typical Wolff-Parkinson-White complexes alternating with periods of normal conduction. The electrocardiogram of yet another subject, whose previous tracing had been normal, contained two short periods of a curious arrhythmia which began with one or two beats showing short P-R intervals and widened QRS complexes and continued as an idioventricular rhythm without recognizable P waves. Prinzmetal and co-workers[5] present evidence to show that this is a variant of the "accelerated conduction" syndrome, while Dressler and Roesler[6] show a similar tracing which they explain as ventricular fusion beats followed by relatively slow ventricular tachycardia. We have observed five other persons with a similar arrhythmia, two of whom have coronary artery disease while the remainder are apparently in good health.[7]

Premature Beats. Thirteen men were reexamined whose electrocardiograms in 1940 showed premature contractions: five atrial, two nodal, and six ventricular. The electrocardiograms of only two of these men showed extrasystoles at the time of the 1950 examination, one atrial and the other ventricular extrasystoles, but the tracings of five additional men showed premature beats, two atrial and three ventricular, which had not been present in 1940.

Conduction Defects. Atrioventricular and intraventricular conduction defects will be

TABLE 3.—*Distribution of P-R Intervals in 1940 and 1950 Examinations of 639 Subjects*

1950 P-R Interval	1940 P-R Interval																		Total
	0.10	.11	.12	.13	.14	.15	.16	.17	.18	.19	.20	.21	.22	.23	.24	.25	.26	.27	.28	
0.10				1																1
0.11				1																1
0.12	1	1	12	2	8		2	1	1											28
0.13		2	9	8	6	8	8	1												42
0.14		2	13	12	30	12	15	4	3			1								92
0.15			6	11	28	6	26	4	5	3										89
0.16	1		9	14	41	23	41	15	12	3	2									161
0.17	1		3	1	9	9	32	20	23	3										101
0.18				1	10	11	20	10	9	2	6									69
0.19				1	1		5	4	1		2									14
0.20					1	5	5	2	5	1	9	3							1	32
0.21									1						1	1				3
0.22													4							4
0.23																				0
0.24							1				1									2
Total.....	3	5	52	52	134	74	155	61	60	12	20	4	4	0	1	1	0	0	1	639

1940 Mean P-R Interval 0.154, standard deviation 0.022; ±2 SD = 0.110–0.198.
1950 Mean P-R Interval 0.159, standard deviation 0.021; ±2 SD = 0.117–0.201.

TABLE 4.—*Effect of Heart Rate upon Mean Intervals in the 1940 and 1950 Examinations*

Heart Rate	Mean P-R Interval		Mean QRS Duration		Mean Q-T Interval		Corrected* Mean Q-T Interval	
	1940	1950	1940	1950	1940	1950	1940	1950
40–49	0.161	†	0.090	†	0.432	†	0.376	†
50–59	0.158	0.168	0.088	0.088	0.406	0.399	0.387	0.402
60–69	0.155	0.163	0.087	0.086	0.380	0.377	0.392	0.389
70–79	0.150	0.159	0.085	0.085	0.356	0.360	0.396	0.400
80–89	0.144	0.158	0.086	0.086	0.337	0.347	0.401	0.413
90–99	†	0.155	†	0.084	†	0.338	†	0.423

* Corrected using Bazett's formula: $QT_c = \frac{QT}{\sqrt{R - R}}$.
† Less than 30 men in sample.

TABLE 5.—*Change in P-R Interval with Change in Heart Rate. 1940–1950*

Change in Heart Rate	Change in P-R Interval				
	Total		Shorter by 0.02 sec. or more	No change (± 0.01 sec.)	Longer by 0.02 sec. or more
	No.	%			
Slower by 5 beats or more.....	69	100	7%	41%	52%
No change (±5 beats)...	153	100	13%	50%	37%
Faster by 5 beats or more.	417	100	20%	54%	26%

discussed in the sections on P-R interval and QRS duration respectively.

The Intervals

P-R Interval. The 1940 and 1950 distributions of the P-R intervals are presented in table 3. The mean P-R interval increased from 0.154 to 0.159 second, a difference which is statistically significant and which is especially surprising since the increase in the mean heart rate from 64 to 75 should be expected to have an opposite effect.

In order to study the effect of rate upon the P-R interval, the mean P-R was determined for various heart rates in the first and second examinations. Table 4 includes the results of this analysis; the usual decrease in P-R interval with increasing heart rate is seen in both the 1940 and 1950 figures. However, at any given heart rate, the 1950 mean P-R interval is consistently longer than the 1940 mean P-R interval. Further correlations, not presented here, show that this difference is not due to chance or to changes in blood pressure or body weight, and thus the increase may be due to some factor associated with aging. This effect of age upon P-R interval has been described by others and summarized by Lepeschkin.[8]

Although the mean P-R interval decreased as rate increased, this was not true in each

TABLE 6.—*Distribution of QRS Duration in 1940 and 1950. Examinations of 639 Subjects*

1950 QRS Duration	1940 QRS Duration							Total
	0.06	0.07	0.08	0.09	0.10	0.11	0.12	
0.05	1							1
0.06		2						2
0.07	2	11	32	1	1			47
0.08	1	26	192	103	5			327
0.09			51	52	52	1		156
0.10			1	24	49	13		87
0.11					6	9		15
0.12							4	4
Total	4	39	276	180	113	23	4	639

1940 Mean QRS Duration 0.087, standard deviation 0.010; ±2 SD = 0.067–0.107.

1950 Mean QRS Duration 0.085, standard deviation 0.096; ±2 SD = 0.066–0.104.

individual case. Table 5 illustrates the frequency of change in P-R interval for those whose heart rates increased, decreased, or changed less than 5 beats per minute. It will be noted that in 26 per cent of the men whose rates increased, the P-R interval lengthened 0.02 second or more and, conversely, in 7 per cent of men whose rates slowed, the P-R interval shortened by 0.02 second or more.

The clinician's interest generally centers about P-R intervals shorter than 0.12 second or longer than 0.20 second. All eight instances of short P-R intervals in 1940 became normal by 1950, while in two previously normal records short P-R intervals developed. (The two cases of Wolff-Parkinson-White syndrome are not included.) On the other end of the scale, 6 of the 11 instances of long P-R intervals still showed first degree atrioventricular block. Of the five instances in which shortening took place, four shortened only to 0.20 second. First degree atrioventricular block appeared in three previously normal tracings. Within the normal range of P-R interval there were 50 instances in which a change of 0.04 second or more occurred. Clinical evidence of heart disease had not developed in any of the men with electrocardiograms showing short or long P-R intervals or a marked change in P-R interval within the normal range.

QRS Duration. The QRS duration was measured* only in the limb leads in order to conform with the measurements made in the first study as well as with the New York Heart Association recommendations.[10] There was a notable constancy of the QRS duration in the individual electrocardiograms with but 10 instances of a variation greater than 0.01 second between records (table 6). In 2 of these 10 tracings the QRS duration had increased. In one instance the QRS duration increased from 0.06 to 0.08 second with the development of the $S_1S_2S_3$ pattern; this pattern has been ascribed to a focal delay in depolarization of the crista supraventricularis of the right ventricle[11] and is generally assumed to be a congenital anomaly. Although this case does not fulfill the criteria for complete or incomplete bundle-branch block, it is conceivable that the development of the $S_1S_2S_3$ pattern in a middle aged man has the same significance as the appearance of right bundle-branch block. In the second instance the QRS duration was 0.10 second with normal configuration in 1950; the 1940 electrocardiogram was missing, but the QRS duration was recorded as 0.08 second. There were eight electrocardiograms with QRS duration apparently shorter than in 1940 by 0.02 to 0.03 second. In some cases the shortening may have been an artefact caused by factors in technic. In other cases the shortening was due to the disappearance of small Q or S waves caused by a shift in the cardiac electrical field.

QRS durations of 0.11 second in leads

* Faulty electrocardiographic technic was most noticeable during attempts to measure the QRS duration. Sixty cycle interference was the most common fault, but careful study of the QRS complex with a hand lens usually made possible an accurate measurement. A more serious fault was found in many of the tracings obtained from direct-writer electrocardiographs, especially those with poorly adjusted styluses: Slight delay of the stylus in leaving the baseline and a poor response to low-voltage, high-frequency waves often completely obscured small Q and S waves and resulted in a falsely short QRS duration. Only when such records were compared with the technically excellent tracings obtained 10 years earlier was it possible to interpret correctly the exact limits of the QRS complex. Lepeschkin[9] has recently discussed the difficulties inherent in the measurement of the QRS duration, and we concur in his statement of the problem.

plainly showing Q, R, and S waves without slurring or notching suggestive of bundle-branch block are occasionally found among healthy individuals; there were 23 such instances in this series. In nine of the 23 tracings the QRS duration remained unchanged, while in 14 it was 0.01 to 0.02 second shorter, probably because rotation of the cardiac electrical field caused the initial or terminal forces to become isoelectric in the limb leads. For the same reasons, in six other instances the QRS duration lengthened from 0.10 to 0.11 second. All these men were in apparent good health.

QRS durations of 0.12 second and greater are rare among healthy individuals, but we were able to follow four apparently healthy men whose electrocardiograms demonstrated prolonged intraventricular conduction. None of these tracings had changed in 1950. The electrocardiograms were characterized by Q, R, and S waves in leads II and III which did not appear abnormal until careful measurement of the QRS complex revealed its surprising width. These men were all asymptomatic, and three of them were naval aviators on active duty.

The constancy of the QRS duration is demonstrated both by the lack of change in the mean QRS (0.087 second in 1940 against 0.085 second in 1950) and in the standard deviation (0.10 against 0.096).

The effect of rate upon the mean QRS duration is shown in table 4. There is a tendency for the mean QRS duration to shorten with increase in rate, but the change is slight over this narrow range in rate, and the differences are not statistically significant at the five per cent level of probability. There was no change over the 10 year period in mean QRS durations at any given heart rate, in contrast to the change noted in the P-R interval with increasing age.

Three instances of bundle-branch block which were excluded from the statistical analysis are worthy of additional comment. In one case the electrocardiogram of a 40 year old pilot in apparently good health changed from normal, with a QRS duration of 0.09 second, to the typical pattern of complete right bundle-branch block (QRS duration 0.13 second). Because of the relative stability of the QRS duration in the majority of the subjects, he will be followed with the expectation that the marked changes in QRS duration may represent the first signs of cardiac disease. Another case of interest was that of a 37 year old pilot whose electrocardiograms are shown in figures 3*A* and 3*B*. Complete right bundle-branch block developed within seconds after he was startled by a pistol shot during the initial study, and the block persisted for several days. Many electrocardiograms in 1952 and 1953 showed transient right bundle-branch block although this disorder had not caused symptoms nor affected his career as an aviator. Occasionally, the tracings showed the bundle-branch block appearing or disappearing; the phenomenon was not associated with a critical heart rate, oxygenation, or other known factors. The portions of the tracings showing normal conduction have not changed over the 12-year period; the same is true of his records which show bundle-branch block. Undoubtedly, the most striking electrocardiogram in the original study was the one showing complete left bundle-branch block which was obtained from a healthy 29 year old aviator (fig. 4*A*). His second electrocardiogram was unchanged after twelve and one-half years (fig. 4*B*). He was asymptomatic and still active as a pilot.

Q-T Interval. The distribution of uncorrected Q-T intervals in 1940 and 1950 is presented in table 7. The mean Q-T interval has decreased from 0.384 second to 0.361 second, a change which is expected because of the increase in mean heart rate from 64 to 75. In table 4 the effect of heart rate upon the mean Q-T interval is demonstrated; it will be noted that with increasing heart rate the mean Q-T interval decreased in both 1940 and 1950 and that the mean Q-T intervals for any given heart rate are about the same on the two examinations. This is in contrast to the mean P-R interval which shows an increase with increasing age as well as a decrease with more rapid rates. Although the mean Q-T interval decreases with increasing heart rate, the

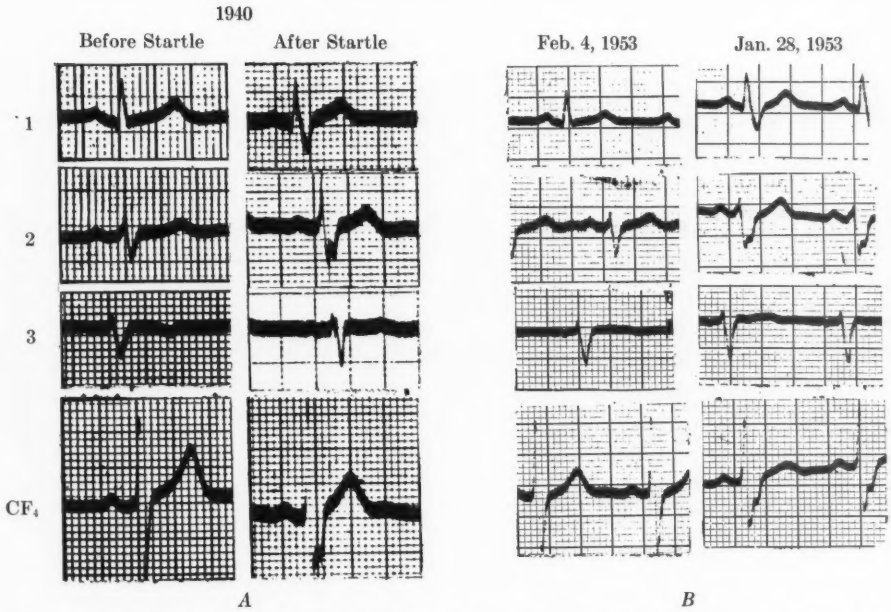

FIG. 3A. The 1940 electrocardiogram of a healthy aviator showing the development of complete right bundle-branch block following startle. (*B*) Electrocardiograms obtained from the same man while at rest on two different occasions in 1953 showing transient complete right bundle-branch block. Subject still a pilot, without symptoms, 12½ years after transient right bundle-branch block was first demonstrated.

individual Q-T measurements show a wide variation and not infrequently lengthen with more rapid rates and shorten with slower rates.

The effect of heart rate upon the mean Q-T interval corrected by Bazett's formula[12] is also included in table 4. With increasing rates the mean corrected Q-T interval ($Q\text{-}T_c$) lengthens slightly; the mean $Q\text{-}T_c$ values of 0.391 for 1940 and 0.403 for 1950 are in line with other reports, as compiled by Lepeschkin.[8]

The Waves

P Waves. The P waves in most cases remained unchanged (fig. 2*A*) although in rare cases notches disappeared or appeared. In one instance the first electrocardiogram was characterized by inverted P waves in leads II and III, and the same configuration was still present 11 years later. Detailed measurements of the P waves were not carried out in the second study.

QRS Deflections. The majority of the changes observed in the ventricular deflections were related to changes in the position of the cardiac electrical field. The mean QRS axis in the first study was +61.6 degrees as shown in table 8, with a range of −35 to +120 degrees. Only 10 electrocardiograms (0.2 per cent) showed electrical axes of less than 0 degrees, and in eight the axis was greater than 90 degrees (fig. 5). In the second study the mean QRS axis was +48.2 degrees with a range of −45 to +95 degrees. The electrical axis in 27 (4.3 per cent) of the electrocardiograms was less than 0 degrees but over 90 degrees in only one. The second electrocardiograms of the eight subjects, whose first electrocardiograms had axes of greater than 90 degrees, all had axes of 90 degrees or less. The magnitude of the changes in QRS axis is shown in table 9 and figure 6. The electrocardiograms of 195 (30.9 per cent) of the subjects showed no change of electrical axis. In the electrocardiograms of 386 of the subjects (61.2 per cent) a counterclockwise or minus deviation of electrical axis had occurred: In the majority (332

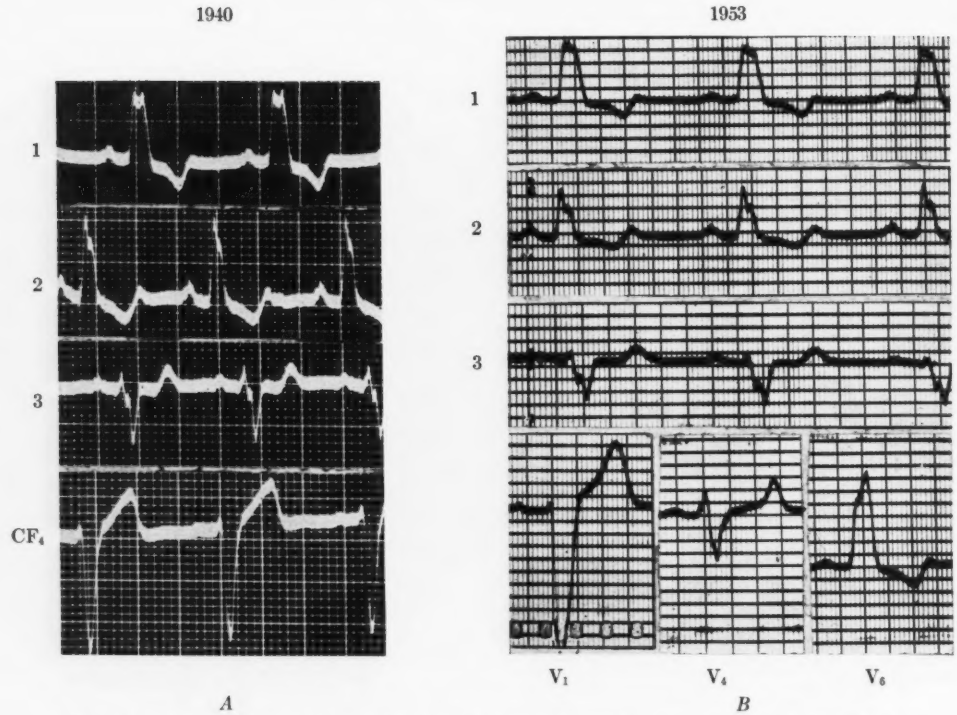

FIG. 4*A* and *B*. Left bundle-branch block persisting unchanged over a 12 year period in a healthy aviator. Note that the paper speed is 40 mm. per second in the 1953 record.

TABLE 7.—*Distribution of Q-T Intervals in 1940 and 1950 Examinations of 639 Subjects*

1950 Q-T Interval	1940 Q-T Interval																					Total
	0.28	.29	.30	.31	.32	.33	.34	.35	.36	.37	.38	.39	.40	.41	.42	.43	.44	.45	.46	.48	.50	.52	
0.28											2						1						3
0.30					1	1			3														5
0.31								1			1		1										3
0.32	1			1	7	1	11	3	20	1	15	2	13	5	4		8						92
0.33					1		1	2	6	2	5	1	6		2		2		1				29
0.34			1		4		4	1	9	4	4		13	2	5	1	1		1				50
0.35			1		1	2	1		4	2	8		5	2	6				1				33
0.36	1			2	16	3	19	1	43	4	28	6	42	5	22	2	10	1	1	1			207
0.37			1		1			1	8	4	9	1	6		5		2						38
0.38					1		2	2	7	1	14		12	1	6		5	1					52
0.39					1		1		2	1	3	1	8	2	3		1						23
0.40			1		1	1	2		16	2	10	2	17	1	8	4	8	1	1	2	1	1	79
0.41						1				1			1		1								4
0.42										1	2		3		2		1					1	10
0.43							1		1		1							1		1			5
0.44											1		1	1			1		1			1	6
Total	2	0	4	3	34	9	42	11	119	23	103	13	128	19	64	7	40	4	6	4	1	3	639

1940 Mean Q-T Interval 0.384, standard deviation 0.035; ±2 SD = 0.314–0.454.
1950 Mean Q-T Interval 0.361, standard deviation 0.029; ±2 SD = 0.303–0.419.

TABLE 8.—*Mean QRS and T Axes and QRS-T Angle in 1940 and 1950. Examinations of 639 Subjects*

	1940	1950	Change
QRS	+61.6°	+48.2°	−13.4°
T	+42.6°	+40.7°	−1.9°
QRS-T	+19.0°	+7.5°	−11.5°

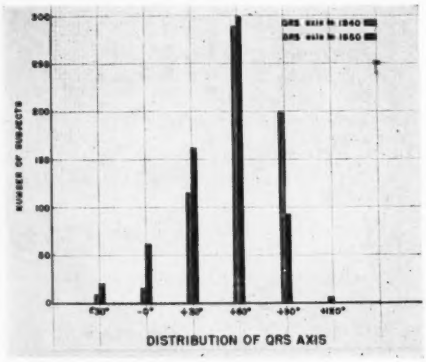

FIG. 5. Distribution of QRS axis of the electrocardiograms obtained in 1940 and in 1950 from 631 subjects.

TABLE 9.—*Relationship of Electrical Axis of QRS in 1940 to the Change in QRS Axis*

1940 QRS Axis	Total	Change in QRS Axis								
		Counterclockwise				±5°	Clockwise			
		−60°	−45°	−30°	−15°		+15°	+30°	+45°	+60°
−30°	8					5	1	2		
−15°	2				1	1				
0°	6			2	2	2				
+15°	16	1	4	1	8				2	
+30°	65		3	17	8	29	1	6		1
+45°	84	3	9	8	29	17	18			
+60°	156	8	6	33	37	60	10	2		
+75°	181		14	22	87	51	7			
+90°	105	4		29	42	30				
+105°	6		1	2	3					
+120°	2	1		1						
Total	631*	17	37	115	217	195	37	10	2	1

* No QRS axis obtainable in eight subjects.

or 91.0 per cent of the 386) the shift was −30 degrees or less, but in 17 instances (2.7 per cent of the 386) was −60 degrees. In only 50 subjects (7.9 per cent) had clockwise or plus deviation of the electrical axis occurred.

Inspection of table 9 reveals that counter-

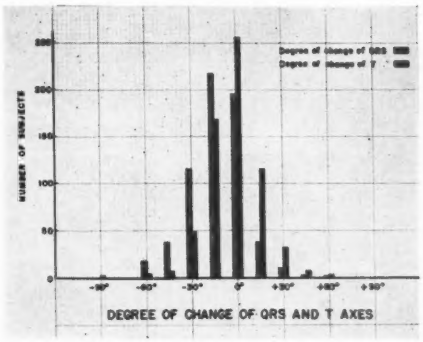

FIG. 6. Degree of change over a 10 year period in the QRS and T axes of the electrocardiograms.

clockwise shift of the axis occurred more often than clockwise, regardless of the position of the axis in 1940, with the exception of the eight electrocardiograms in which the QRS axis was deviated markedly to the left (−30 degrees) in the first study. Furthermore, the most marked (−60 degrees) counterclockwise shifts did not occur predominately in those persons whose electrocardiograms had shown the most rightward positions in the first study.

Neither the position of the electrical axis of QRS nor the change in axis was related to the level of systolic or diastolic blood pressure. Height was a definite but minor factor in the position of the axis, with tall persons having more rightward positions. Absolute weight was a major factor in the position of the QRS axis in both studies, with heavier persons having more leftward positions. The change of axis was related to change in weight, increasing weight tending to deviate the axis to the left.

Of the 10 subjects with axes of less than 0 degrees in the first study, eight remained less than 0 degrees. These electrocardiograms were all characterized by an rS complex in leads III and aV_F and a qR complex in leads aV_L and I (counterclockwise frontal QRS vectorcardiogram) with normal T deflections. The stability of this particular pattern over the 10 year period suggests that marked left axis deviation with this configuration need not be regarded as abnormal.

As a result of the incidence of the shift of the mean electrical field in a counterclockwise direction, there occurred an increase in the

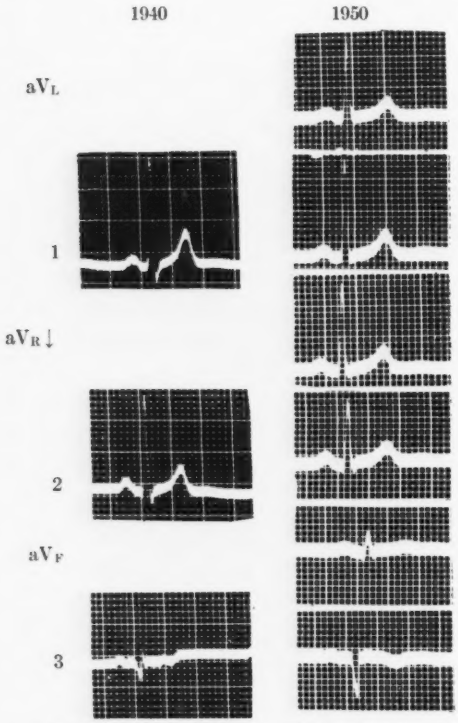

FIG. 7. Electrocardiograms illustrating the effect of a counterclockwise shift of QRS forces (deviation of electrical axis to the left) on the Q wave in lead III: 1940, QRS axis +30 degrees; clockwise QRS frontal vectorcardiogram with deep, wide Q_3. 1950 QRS axis +10 degrees; marked increase in depth of Q_3, decrease in R_3 and S_1. The leads of the 1950 electrocardiogram are mounted according to the angular relationships of their axes, and the polarity of aV$_R$ is reversed.[17]

number of electrocardiograms in which the configuration of the QRS deflections in lead III was rS rather than Qr. In rare instances a qR complex in lead III (clockwise frontal vectorcardiogram) had changed into a Qr_3, but in none of these cases was the electrical axis less than +10 degrees; the most marked change of this kind is shown in figure 7. In the 1940 electrocardiogram the electrical axis was approximately +30 degrees, and a QR occurred in lead III. In the 1950 electrocardiogram the axis was +10 degrees, and a Qr occurred in lead III. In none of the subjects whose electrocardiograms showed a deep, broad Q_3 with an inverted T_3 in the first study

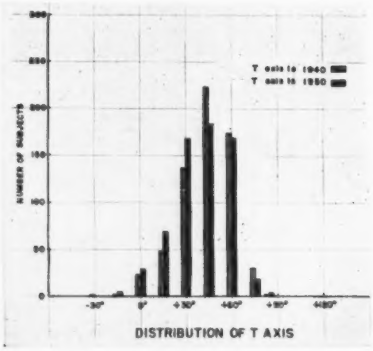

FIG. 8. Distribution of T axis of the electrocardiograms obtained in 1940 and in 1950 from 639 subjects.

had heart disease become manifest in 1950. In none of the electrocardiograms in the second study was the Q of lead aV$_F$ greater than the R of this lead, and in no case was a Q of lead aV$_F$ wider than 0.04 second.

Almost without exception the electrocardiographic leads were qualitatively similar in the two studies; the QRS pattern observed in each of the leads in the first study tended to persist, although quantitative changes in the ratios of the amplitudes of the various deflections to each other commonly occurred, especially in lead III.

T Deflections. The mean electrical axis of T observed in the first study was +42.6 degrees and the range was −30 to +85 degrees; in only one electrocardiogram was the T axis greater than +75 degrees (T of aV$_L$ more negative than T of lead I positive), and in only two, less than 0 degrees (T of lead III and aV$_F$ inverted). (See fig. 8.) The mean T axis in 1950 had changed only 1.9 degrees in a counterclockwise or minus direction to +40.7 degrees; the range of the T axes in the second study was from −20 to +85 degrees; in only two electrocardiograms was the T axis greater than +75 degrees and in only four cases less than 0 degrees.

The T axis did not change in the electrocardiograms of 255 (39.9 per cent) subjects, deviated in a counterclockwise or minus direction in 228 (35.7 per cent), and in a clockwise or plus direction in 156 (24.4 per cent). These changes in the T axis are compared

TABLE 10.—*Relationship of Electrical Axes of QRS and T in the 1940 Examinations of 631* Subjects*

T Axis	QRS Axis											Total
	−30°	−15°	0°	+15°	+30°	+45°	+60°	+75°	+90°	+105°	+120°	
−30°	1											1
−15°					1	1		2				4
0°	1	1	1	3	5	5	5	1				22
+15°	1	1		3	10	8	12	6	7			48
+30°	3			4	18	31	39	25	14	2		136
+45°	1		4	4	20	30	72	61	26		2	220
+60°	1		1	2	11	9	26	75	43	4		172
+75°							2	10	15			27
+85°								1				1
Total.....	8	2	6	16	65	84	156	181	105	6	2	631
Mean T.....	+23°	+8°	+40°	+29°	+34°	+35°	+40°	+49°	+51°	+50°	+45°	

* No QRS axis obtainable in eight subjects.

TABLE 11.—*Relationship of Electrical Axes of QRS and T in the 1950 Examinations of 631* Subjects*

T Axis	QRS Axis										Total
	−45°	−30°	−15°	0°	+15°	+30°	+45°	+60°	+75°	+90°	
−45°											0
−30°											0
−15°			1			1			1	1	4
0°		2	3	10	1	4	2	5	1	1	29
+15°		2	5	9	9	14	6	17	3	2	67
+30°	1	3	3	10	4	48	27	47	19	5	167
+45°		4	2	8	2	30	29	65	29	13	182
+60°		1		7	3	18	7	78	33	15	162
+75°								1	13	4	18
+85°					1	1					2
Total.....	1	12	14	44	20	116	71	213	99	41	631
Mean T.....	+30°	+30°	+17°	+28°	+31°	+36°	+37°	+44°	+49°	+48°	

* No QRS axis obtainable in eight subjects.

with those of QRS in figure 6; less change occurred in the T axes than in the QRS axes, and deviations in a clockwise as well as in a counterclockwise direction frequently occurred.

Marked lowering of the voltage of the T waves in both the limb and chest leads was noted in two instances. This change in voltage was not accompanied by an appreciable change in the direction of the T axis and could not be correlated with any change in the clinical status of the two men. The future health of these subjects will be followed with more than ordinary interest.

QRS-T Relationship. The relationships of the electrical axes of QRS and T in the two studies are presented in tables 10 and 11; the averages of the T-axis positions for each of the QRS axis positions are shown on the bottom line of the tables. In accord with previous experiences, inversion of T_3 (T axis less than +30 degrees) was found more commonly with more counterclockwise positions of the QRS axis (horizontal electrical position). Conversely, inversion of T in aV_L (T axis greater than +60 degrees) was more common with the more clockwise positions of the QRS axis (vertical electrical position). T-axis deviations of greater than +75 degrees or less than 0 degrees, however,

not only occurred rarely but were not clearly related to marked deviations of the QRS axis.

The mean angle between the QRS and T axes, the QRS-T angle, found in the two studies is shown in table 8. From inspection of tables 10 and 11 this angle may be calculated for the various QRS positions, and it will be noted that it was greatest when marked left or right axis deviation of QRS was present. In 98 per cent of the electrocardiograms in 1940 and 1950 the QRS-T angle was +60 degrees or less. In 77 per cent of the electrocardiograms in 1940 the T axis was counterclockwise to the QRS axis (positive QRS-T angle); in 11 per cent QRS-T equalled 0, and in 12 per cent the T axis was clockwise to the QRS axis (negative QRS-T angle). In 66 per cent of the electrocardiograms the same relationship obtained in the 1950 records. A detailed study of the QRS-T relationships in the electrocardiograms of these and other healthy persons will be presented later.[13]

RS-T Segment

RS-T segment depressions greater than 0.5 mm. were not encountered in either study with the exception of the case of left bundle-branch block and the cases of the Wolff-Parkinson-White syndrome. One subject presented a peculiar flattening of the RS-T segment with low T waves reminiscent of an electrocardiographic abnormality found in a southern family.[14]

Precordial Leads

Precordial leads CF_4 and CR_4 were used during the first study whereas the second study utilized leads V_1 through V_6. Although direct comparison between the two was not possible, marked differences were not found between CF_4 and V_4. In only one case did abnormalities show up in the chest leads which were not evident in the limb leads. In this one case a QS pattern was found in leads V_1, V_2 and V_3 suggesting an old anterior myocardial infarction. However, the limb leads were normal and unchanged over the 10 year period; CR_4 and CF_4 in 1940 closely resembled V_4 in 1950. The subject had had no symptoms suggesting an infarction, and it therefore seems likely that the same configuration in V_1, V_2 and V_3 might have been present in 1940 had these leads been taken.

The Influence of Certain Physiologic Variables

An attempt was made to measure the effect of change in age, weight, heart rate, and blood pressure on the electrocardiogram in the case of subjects who had normal records on both examinations. It was found that the QRS duration was not affected; the Q-T interval showed the expected change with heart rate, which could partially be corrected by using Bazett's formula, but was unaffected by increase in age, body weight, or blood pressure; the P-R interval, on the other hand, lengthened with increasing age but was not affected by body weight or changes in blood pressure. The effect of heart rate upon P-R interval is well known. Although our data confirm this relationship for the group as a whole, it was somewhat surprising to find the wide individual variations. The direction of the QRS axis was found to shift counterclockwise with increasing age, probably because of simultaneous increase in weight. The height of the subject also was a factor in determining the original position of the QRS axis, but blood pressure within the normal range was not a factor. The change in T axis was slight and not definitely related to these factors or regularly related to the change in QRS axis. Our data support those recently published by Simonson and Keys.[15] A more extensive study on the importance of these variables on the form of the electrocardiogram will be the subject of a forthcoming report.

In table 12 we have compiled proposed "ranges of normal" for various measurements at different heart rates. Each range includes 96 per cent of the observations (plus or minus two standard deviations from the mean). These ranges vary only slightly from those in common use.

Correlation of the Electrocardiographic Findings with Other Signs and Symptoms of Heart Disease

For this purpose the electrocardiograms were divided into three categories, namely, abnormal, borderline, and normal. The subjects,

TABLE 12.—*Proposed "Range of Normal" for Men 20–30 and 30–40 Years of Age*

Heart Rate	P-R Interval		QRS Duration		Q-T Interval		Corrected Q-T Interval	
	20–30 Years	30–40 Years	20–30 Years	30–40 Years	20–30 Years	30–40 Years	20–30 Years	30–40 Years
40–49	0.120–0.200	*	0.070–0.110	*	0.355–0.505	*	0.305–0.480	*
50–59	0.110–0.205	0.125–0.210	0.070–0.105	0.065–0.110	0.355–0.455	0.350–0.450	0.335–0.440	0.350–0.450
60–69	0.110–0.200	0.120–0.205	0.065–0.105	0.065–0.105	0.330–0.430	0.330–0.425	0.340–0.440	0.340–0.440
70–79	0.110–0.195	0.120–0.200	0.065–0.105	0.065–0.105	0.310–0.400	0.315–0.415	0.350–0.440	0.355–0.445
80–89	0.110–0.180	0.120–0.200	0.065–0.105	0.065–0.105	0.295–0.380	0.300–0.395	0.355–0.445	0.360–0.460
90–99	*	0.115–0.195	*	0.065–0.100	*	0.295–0.380	*	0.380–0.465
All heart rates	0.110–0.200	0.115–0.200	0.065–0.105	0.065–0.105	0.315–0.455	0.305–0.420	0.320–0.460	0.345–0.460

* Less than 30 subjects.

of course, cannot be classified on an absolute basis of heart disease or no heart disease but only on the basis of symptomatology. The following comments relate to the 645 subjects with complete records on both examinations.

At the time of the 1940 examinations none of the subjects had symptoms suggestive of possible heart disease; three of the electrocardiograms were abnormal, 90 borderline, and 552 normal. No cardiovascular symptoms developed in the three subjects with abnormal records in 1940. The absence of complaints in the subject whose electrocardiogram showed short P-R interval and wide QRS waves is not remarkable even though patients with the Wolff-Parkinson-White syndrome have a death rate above the normal.[16] In the subject with intermittent right bundle-branch block, and especially in the subject with left bundle-branch block, underlying heart disease is a possibility if not a probability. It is well known that these may be signs of heart disease even in the absence of any other signs or symptoms.

None of the 90 subjects with borderline electrocardiograms were found to have other signs or symptoms suggestive of heart disease during the follow-up period. Moreover, in 59 of the 90 instances the borderline alteration disappeared, and in the remaining 31 instances none of the alterations progressed in the direction of greater abnormality. These facts indicate without question that the borderline findings did not represent a stage in the transition from a normal to an abnormal electrocardiogram. Furthermore, these facts strongly suggest that the majority of the borderline findings were innocent. However, a longer follow-up period is necessary to decide which if any of the borderline alterations have pathologic significance.

The only subjects who were found to have cardiac signs and symptoms during the follow-up period were in the group who had normal electrocardiograms in 1940. Four showed definite signs of heart disease but in only one of these (the case of myocardial infarction) did the electrocardiogram become abnormal. Moderate hypertension developed in 12, and in 8 additional subjects the size of the heart as determined by x-ray measurement was above the upper normal limit; no significant change had developed in the electrocardiograms of these 20 men and none had any subjective complaints. In 19 other instances a significant change occurred in the electrocardiogram: Borderline abnormalities appeared in 17 tracings; right bundle-branch block in one, and intermittent short P-R intervals and wide QRS complexes in one. None of these 19 subjects had other evidence suggesting heart disease, but their future course will be followed with more than ordinary interest.

DISCUSSION

The present study not only provides additional observations on the range of values found in the electrocardiograms of healthy individuals but also permits certain conclusions regarding the reliability and validity of clinical electrocardiography.

Reliability refers to the degree of similarity between electrocardiograms obtained over a period of time from the same individual in continual good health. A high degree of reliability depends upon an unchanged response

of the electrocardiograph and upon the accuracy of the technic with which it is used as well as upon lack of physiologic alterations in the individual. In 40 per cent of the 645 individuals with two electrocardiograms taken 10 years apart, the two tracings were nearly identical; in 52 per cent the records were similar, and any differences could be ascribed to physiologic changes such as heart rate or body weight. There were thus 92 per cent of the electrocardiograms which were identical or nearly so. We regard this as an excellent testimony to the reliability of the method especially when it is realized that, in addition to whatever unknown physiopathologic changes might have occurred in the individual subject, the electrocardiograms were obtained under widely differing environmental circumstances by many operators using various types of electrocardiographs. These findings support the conclusion that an electrocardiogram obtained at an early period in life, the so-called "baseline electrocardiogram," is valuable for future comparison.

There were 8 per cent of the cases in which comparison of the two tracings revealed significant differences. In a few instances the changes could be attributed to the development of definite or probable heart disease, but in the majority the differences consisted in the inexplicable appearance or disappearance of borderline variations. Although this probably indicates a lack of reliability in the electrocardiographic method, it is also possible that otherwise unrecognizable heart disease may be the cause of these differences in the two records, a possibility which leads us to a discussion of the validity of the electrocardiogram.

Validity in clinical electrocardiography is concerned with the regularity of the association of abnormal records with the presence, and normal records with the absence, of heart disease. Although certain patterns of electrocardiographic variation are related in greater or less degree to specific types of cardiac defect or disorder, the validity is generally recognized to be poor, for a normal tracing is frequently obtained from a person with definite heart disease and, less often, an abnormal record is obtained from an apparently healthy individual.

Our experience, as summarized in the previous section, confirms the lack of validity of the electrocardiographic method. Of four men with definite heart disease, only one had an abnormal electrocardiogram, and of 20 men with possible heart disease as evidenced by hypertension or enlarged hearts, none had an abnormal electrocardiogram. Conversely, a number of men with borderline or frankly abnormal tracings have no other subjective or objective evidence of heart disease. Although these men have been followed for a period of at least 10 years, making latent heart disease unlikely, a final answer must await additional periodic examinations.

Summary

1. Ninety-six per cent of a group of 1000 healthy aviators whose electrocardiograms were analyzed in 1940–1942 were traced after an interval of at least 10 years.

2. Two hundred and two men had died. Trauma caused 193 deaths, disease seven, and the cause was unknown in two. Only one man died of heart disease (myocardial infarction); his electrocardiogram had been normal in 1941.

3. Seven hundred and three men were reexamined and only four were found to have objective evidence of heart disease: One had coronary heart disease with myocardial infarction, two had hypertensive heart disease, and one had chronic cor pulmonale. Eight other men showed enlargement of the heart by x-ray examination, without other evidence of heart disease. Twelve others had blood pressures greater than 145/95 mm. Hg with otherwise normal findings.

4. In 639 men the 1940 and 1950 electrocardiograms were subjected to statistical analysis. The heart rate increased from a mean of of 64 to 75 beats per minute, the mean P-R interval increased from 0.154 second to 0.159 second despite the increased heart rate; the mean QRS duration changed only slightly from 0.087 second to 0.085 second, and the mean uncorrected Q-T interval decreased from 0.384 second to 0.361 second. The QRS axis (mean frontal plane QRS vector) shifted to the left from 61.6 degrees to 48.2 degrees, and the T axis (mean frontal plane T vector) likewise

moved slightly to the left from 42.6 degrees to 40.7 degrees.

5. The effect of change in heart rate, age, weight, and blood pressure on these electrocardiographic measurements is discussed. On the basis of these findings ranges of normal are proposed which vary only slightly from those suggested by other authors.

6. Certain unusual cases were not included in the statistical analysis but are described briefly. These include two instances of the Wolff-Parkinson-White syndrome, two instances of complete right bundle-branch block, and one instance of complete left bundle-branch block.

7. There was a wide range of measurements of the electrocardiograms of these healthy men but in the individual cases the change over a 10-year period was relatively slight. This was true both for the normal electrocardiograms and for those which fell in the borderline zone between normal and abnormal. The reliability and validity of the electrocardiographic method is discussed in the light of these findings.

Sumario Español

1. Noventa y seis por ciento de un grupo de 1000 aviadores saludables cuyos electrocardiogramas fueron analizados en 1940–42 fueron trazados luego de un intervalo de no menos de 10 años.

2. Docientos dos hombres murieron. Trauma causo 193 muertes, enfermedad siete y la causa fué desconocida en dos. Solamente un hombre murió de enfermedad cardíaca (infarto del miocardio); su electrocardiograma fué normal en 1941.

3. Setecientos tres hombres fueron re-examinados y solo cuatro fueron hallados tener evidencia objetiva de enfermedad cardíaca: Uno tenía enfermedad coronaria con infarto del miocardio, dos tenían enfermedad hipertensa cardiovascular y uno tenía cor pulmonale crónico. Ocho otros hombres mostraron engrandecimiento del corazón al examen radiológico, sin otra evidencia de enfermedad cardíaca. Doce otros tenían presiones arteriales más altas que 145/95 mm. de Hg con hallazgos normales por lo demás.

4. En 639 hombres los electrocardiogramas de 1940 y 1950 fueron sujetos a análisis estadístico. El pulso aumentó de un promedio de 64 a 75 pulsaciones por minuto, el intervalo P-R aumentó de 0.154 segundos a 0.159 segundos no obstante el aumento en pulso; el promedio de duración de QRS cambió muy ligeramente de 0.087 segundos a 0.085 segundos y el promedio de intervalos Q-T no corregidos disminuyó de 0.384 segundos a 0.361 segundos. El eje QRS (promedio del plano frontal del vector QRS) se movió hacia la izquierda de 61.6 grados ha 48.2 grados y el eje de la T (promedio del plano frontal del vector T) igualmente se movió ligeramente hacia la izquierda de 42.6 grados ha 40.7 grados.

5. El efecto del cambio en el pulso, edad, peso y presión arterial en estas medidas electrocardiográficas se discute. Basado en estos hallazgos se proponen valores normales que varían ligeramente de aquellos sugeridos por otros autores.

6. Algunos casos poco usuales no fueron incluidos en el análisis estadístico pero se describen brevemente. Estos incluyen dos casos del síndrome Wolff-Parkinson-White, dos casos de bloqueo completo de rama derecha y un caso de bloqueo completo de rama izquierda.

7. Hubo una diferencia grande en las medidas de estos electrocardiogramas en estos hombres jovenes pero en los casos individuales durante un período de 10 años la diferencia fué muy ligera. Esto fué cierto en ambos, en los electrocardiogramas normales y en aquellos que cayeron en la colindancia de lo normal y lo anormal. La confiabilidad y la validez del método electrocardiográfico se discute a la luz de estos hallazgos.

Acknowledgments

We are greatly indebted to many persons of good will both within and without the Navy who assisted us in the collection and analysis of the data contained in this report.

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Electrocardiography in the Selection of Royal Canadian Air Force Aircrew

By G. W. MANNING, M.A., M.D., PH.D., F.R.C.P. (C)

The electrocardiograms of 5000 healthy adult male applicants for aircrew training have been reviewed. Abnormalities were observed in the tracings of 158 subjects and these were further investigated. T-wave abnormalities occurred in 95 applicants, prolongation of the QRS (including the Wolff-Parkinson-White syndrome) in 28, prolongation of the P-R interval in 23, and miscellaneous changes in a group of 12 men. In many instances the apparent abnormality could be explained as a variation of normal on repeat study (including multiple lead electrocardiograms). In 27 men (0.54 per cent), 15 of whom revealed some associated clinical cardiovascular findings, a significant abnormality persisted and these were considered as unfit for pilot training.

DURING the first two years of World War II, routine electrocardiograms were taken on all Royal Canadian Air Force aircrew trainees at Initial Training School level. These studies were initiated in order to establish the normal for the age group and to ascertain the value of this procedure in the medical selection of aircrew.[1, 2] Graybiel and his co-workers[3] carried out similar studies. It was soon apparent that many variations, particularly with regard to axis deviation, T-wave amplitudes, and even conduction time, were frequent, depending on cardiac position and physiologic changes.[4, 5] Tracings showing changes beyond the so-called upper limits of normal were studied in some detail and a follow-up study is being carried out on this 1940–42 group. Trainees who were clinically normal were allowed to continue aircrew training regardless of the electrocardiographic abnormality. Studies on the effect of posture and respiration on axis deviation, A-V conduction time and T-wave direction and amplitude were carried out. The effects of posture and deep inspiration on the negative T-waves in lead III were observed. These studies, made before the use of the unipolar limb leads, indicated that the physiologic negative T waves in lead III (due to cardiac position) practically always became upright or showed a decrease in negativity during deep inspiration.[5, 6] Further work on this phenomenon, including the use of the unipolar leads in both the normal and pathologic cases of negative T waves in lead III, is presently being carried out.

Although our follow-up studies are by no means complete, it would appear that certain specific abnormalities in the electrocardiogram should preclude aircrew training. Significant abnormalities that cannot be accounted for by cardiac position and other physiologic variations (known to produce electrocardiographic changes) in the light of our present knowledge in all probability indicate a cardiac disorder.

From earlier studies, and also from the data presented in this report, it is apparent that significant electrocardiographic abnormalities occurring in a large series of healthy young male subjects are indeed rare (0.54 per cent). Not infrequently one finds some cardiac disorder to account for electrocardiographic abnormality when further, more detailed cardiac investigation is carried out. There remains, however, a small group (0.2 or 0.3 per cent) in whom the abnormality in the light of our present knowledge cannot be explained.

Although the significance of many long-standing electrocardiographic abnormalities may be unexplained for many years, the evidence at the present time, including our

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own experience, is that many such abnormalities do frequently indicate a cardiac disorder. There are numerous examples of this. The Wolff-Parkinson-White syndrome for example may be acquired or congenital, and there are a number of case reports now indicating that this electrocardiographic pattern may not be innocent.[7, 8] Paroxymal tachycardia occurs more readily in this group of cases and may give rise to distressing symptoms that could well impair a pilot's ability to handle an aircraft in a crucial maneuver, such as landing or take-off. We have recently encountered a case of Wolff-Parkinson-White syndrome in a 45 year old ex-Royal Canadian Air Force man who in 1943 suffered bouts of paroxysmal tachycardia. He was recently admitted to hospital with symptoms suggestive of cardiac infarction. The electrocardiogram showed a Wolff-Parkinson-White syndrome. The literature contains an increasing number of such cases some of which are of the acquired type due to coronary heart disease[9] and others congenital, later revealing cardiac manifestations.

Again in an earlier series (1940–42) there were 10 examples of abnormal T waves in a series of 2,500 routine electrocardiograms. Although the follow-up is not completed, it is known that some who showed this change revealed clinical evidence of a cardiac disorder within a few years, one such airman (fig. 1) died suddenly one year after the T-wave changes were discovered. This man was in apparent good health and had completed flying training. He was serving with Fighter Command and had made a number of operational flights. He died suddenly as he approached his aircraft for take-off. The cause of death was reported to us as coronary thrombosis. Other examples in addition to those described in this report have occurred in which the electrocardiogram indicated a cardiac disorder not recognized clinically (fig. 2).

It is of course known that coronary heart disease, particularly angina pectoris, can exist in the absence of any detectable electrocardiographic changes (using present routine methods). The incidence of cardiac disease in the presence of significant electrocardiographic

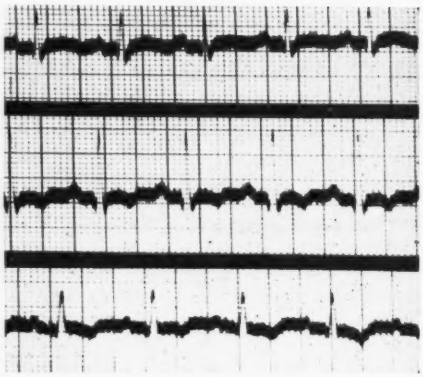

FIG. 1. Fighter pilot, age 27, in apparent good health. Died one year after this tracing was taken. Leads I, II, III. (1941 series.)

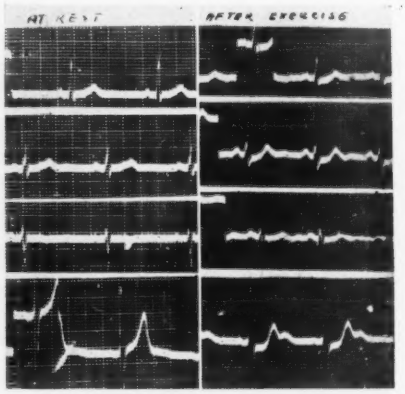

FIG. 2. Transport pilot, age 37, complained of substernal pain in July 1943. Blood pressure normal. Seen by seven cardiologists. History suggestive of angina. Electrocardiogram was normal with low to flat T waves at times. After considerable study eventually cleared as fit. Above tracing shows effects of exercise in October 1944. Died suddenly in 1947 shortly after successfully landing his aircraft.

abnormalities as determined from insurance data, our previous studies, and data collected by commercial airlines and other sources, certainly indicates that an obvious electrocardiographic abnormality should preclude aircrew training.

In view of the very high wastage among aircrew trainees from all causes, every effort is being made to select as far as possible only those likely to become successful. Although the present day selection routine include

many procedures applicable to flying aptitude, medical selection is of course of fundamental importance. When one realizes the performance capabilities of present-day military aircraft, not to consider the high-speed, high-altitude possibilities of the immediate future, it is apparent that our medical selection is of extreme importance not only with regard to wastage during training but with regard to the physiologic stress imposed by modern military flying.

Apart from the risk involved, the financial aspects must be considered. In view of the extremely high cost of aircrew training, it is of considerable economic importance that the man will continue first as a first-line fighter pilot, later as an instructor, and finally in an administrative or educational position as the case may be. If one in every 1,000 were justifiably rejected on the basis of abnormal electrocardiograms, the saving would be well worth while from a purely economic standpoint. On the other hand if all electrocardiographic abnormalities were considered as a cause for rejection then the aircrew manpower wastage might be too high. The purpose of this report is to indicate the frequency of obvious abnormalities occurring in men selected for aircrew training and the importance of considering such abnormalities in the light of the risk involved and also in relation to the economic feasibility of training such men.

Procedure

In this study 5,000 routine electrocardiograms taken on applicants for aircrew training with the Royal Canadian Air Force have been reviewed. In all cases a complete history, physical examination, psychiatric assessment and ophthalmoscopic consultation, in addition to certain aircrew and officer aptitude tests, had been carried out. On the basis of these procedures the candidates were considered as fit for aircrew training. The routine electrocardiogram consisted of leads I, II, III and CF_4. In subjects who showed variations from the so-called normal for these leads, a complete set of standard, unipolar limb leads and leads V_1 to V_6 were recorded, the effects of posture and respiration being investigated when indicated. If the abnormality could not be explained as a normal variation, the man was seen and carefully investigated by a cardiac consultant who usually carried out further electrocardiographic studies. In most instances where the candidate was considered unfit for aircrew training on the basis of the electrocardiographic findings, all aspects were reviewed and further opinions were obtained as to whether such a man should be accepted for aircrew training.

Table 1.—*Routine Electrocardiograms—R.C.A.F. Aircrew Applicants*

Total electrocardiograms read	5000
Number of repeat studies carried out	158
T-wave abnormalities	95
Prolongation of QRS	28
Prolonged P-R interval	23
Miscellaneous	12
Total considered unsuitable for pilot training	27

Results

In 158 of these 5,000 routine electrocardiograms, the initial electrocardiogram was abnormal or showed significant variations from the normal, which suggested repeat studies. There were 95 with T-wave abnormalities, 28 with prolongation of the QRS in its various forms, 23 with prolonged P-R intervals, and a group of 12 with different changes classed as miscellaneous. From this entire group, 27 of these 158 subjects were considered as unsuitable for pilot training (table 1). There were, however, in addition to this, many who showed variations within the so-called normal range. In reviewing these tracings it was again apparent that the so-called textbook "normal tracing" is indeed a rarity, and that minor variations from the so-called classic normal are the rule.

T-Wave Abnormalities

There were 95 of the 158 subjects who showed abnormalities of the T-wave in the initial tracing (table 2). In seven it was apparent from the repeated studies that lead I had been incorrectly recorded during the initial tracing, lead I showing a reversed or "mirror image" pattern.

There were 53 of the remaining 88 subjects with abnormally low or negative T waves in leads I or II, or CF_4 or in a combination of these leads in the initial tracing. In 46 of these, repeat studies showed no clinical findings

TABLE 2.—*T-Wave Abnormalities—95 Cases*

Incorrect lead application	7
Low to negative T_1, T_2 or CF_4 regarded as normal on repeat studies	46
Significant T abnormality persisting on repeat study	7
Q_3T_3 pattern	8
Deep T_3, flat T_2	25
R-T_3,S-T deviation	2

88 cases allowed to continue aircrew training.
62 readily explained on multiple lead study.
26 (14 not repeated) 12 not explained but all clinically normal and passed.

permitted but they were to be followed. It has been suggested that such electrocardiographic variations may be the result of neurocirculatory asthenia. Since this view is open to question and particularly since the electrocardiographic changes considered significant in this study were persistent, the possibility of such functional or physiologic variations has not been considered in this report. It may be noted however, that all men had been carefully studied by experienced psychiatrists as part of the selection procedure, which should tend

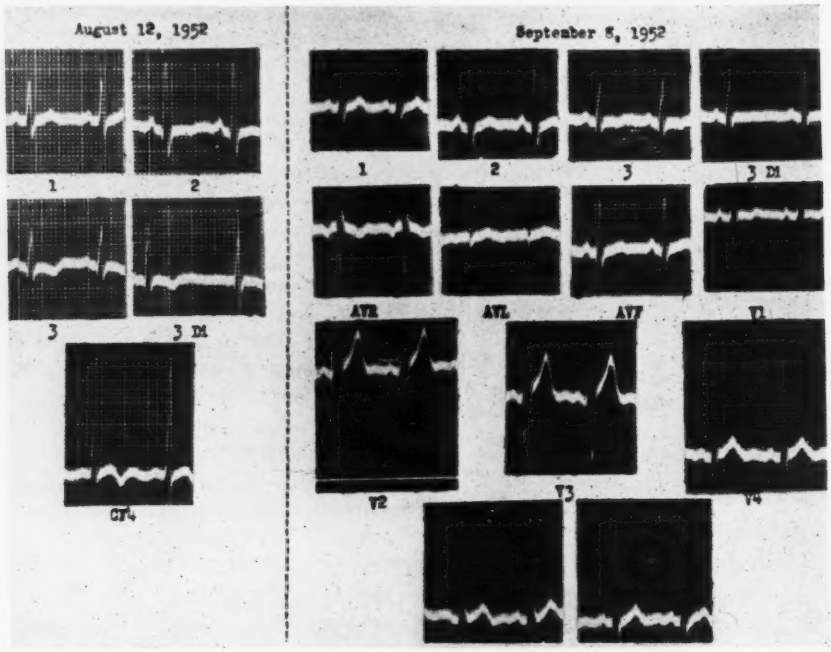

FIG. 3. Aircrew applicant. Left, routine tracing Aug. 12, 1952. Inverted T_2, T_3 and CF_4. No clinical cardiovascular abnormalities. Right, normal tracing on repeat study Sept. 8, 1952.

with regard to the cardiovascular system, and the abnormality on further investigation had either disappeared or could be accounted for when multiple precordial and unipolar limb leads were obtained (fig. 3). In a few subjects, however, the electrocardiograms could not be explained as completely normal tracings after repeat studies, including analysis of QRS and T vectors (fig. 4). Since these were borderline cases and the subjects were completely fit from the clinical aspect, flying training was to minimize such cases in this group. In any event, if the electrocardiographic variation on repeat studies had disappeared or could be satisfactorily explained, the man was considered as fit from the electrocardiographic or cardiovascular standpoint, no consideration being given to the possibility of the electrocardiographic variations being due to neurocirculatory asthenia.

Seven of the 53 subjects referred to in the preceding paragraph continued to show

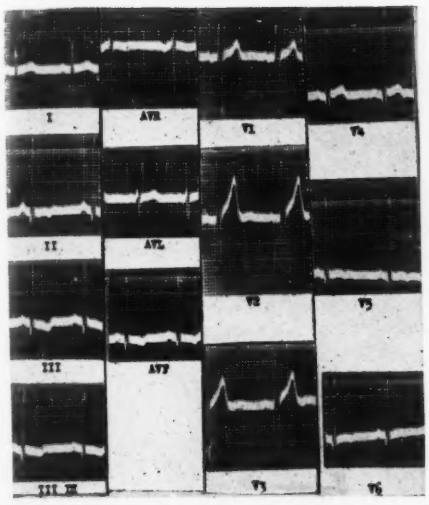

FIG. 4. Aircrew applicant, age 21. Routine tracing showed in lead I, II, III same findings as in this repeat tracing, taken November 1952. A tracing taken November 1953 is unchanged. Completely normal cardiovasular findings.

significant T-wave abnormalities and were considered unfit for pilot training. Five of these seven men on further cardiovascular investigation revealed, in addition to the T-wave abnormality, clinical findings suggestive of a possible cardiovascular disorder (figs. 5 and 6).

There were 33 cases with a deep, negative T wave in lead III. Nine of these showed a Q_3T_3 pattern. Six of these nine subjects could be accepted as having normal electrocardiograms when a complete electrocardiographic study was carried out (fig. 7), in one the abnormality remained (fig. 4) and in the remaining two no further study was obtained. In 24 of these 33 subjects, a deep negative T wave in lead III occurred with either an absent or insignificant Q, most of these presenting a low or flat T wave in lead II. The initial questionable findings in the electrocardiograms of 18 of these 24 subjects could be explained as normal variations due to cardiac position or rotation, when a repeat multiple lead study was carried out; in the remaining six subjects no further study was possible.

A number of examples in the 5,000 tracings

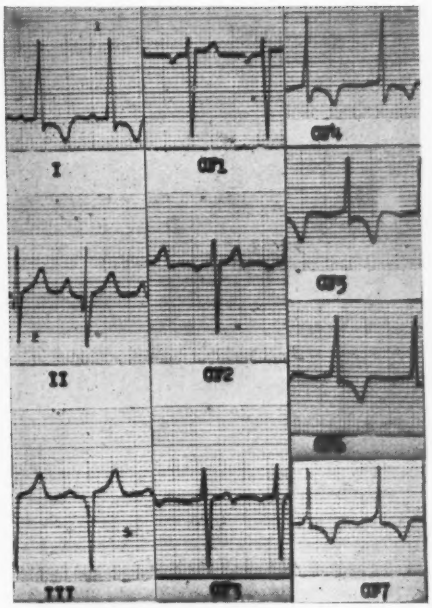

FIG. 5. J. F. G., age 21. Not accepted for aircrew training. Routine tracing showed similar findings to this repeat study taken December 1949. Re-examination showed loud heart sounds, a mid-diastolic triple rhythm or gallop with heart rate of 100, a harsh systolic murmur over apex and along left sternal border. Fluoroscopy was inconclusive but suggestive of left ventricular hypertrophy. Blood pressure 128/74.

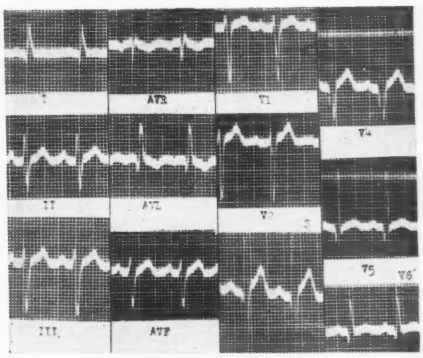

FIG. 6. J. C. M., age 24. Not accepted for pilot training. Routine tracing made in July 1952 was indicative of left ventricular hypertrophy. This repeat study shows same findings. Blood pressure, 120/80. Loud split first heart sound, clear loud third heart sound, and systolic murmur. Heart normal on x-ray examination.

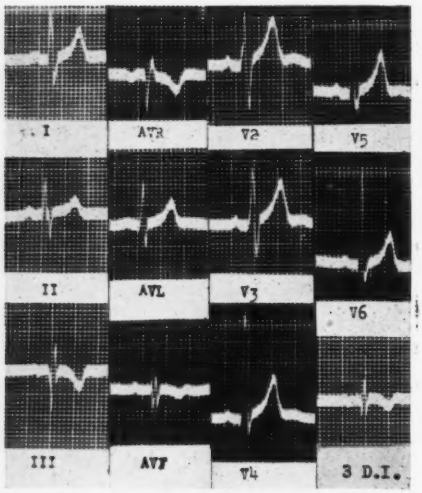

FIG. 7. Aircrew applicant. W. B. B., age 22. Routine tracing leads I, II, III, and CF_4 taken March 1952 showed obvious Q_3T_3 pattern. This repeat series shows this to be normal variation. Note effect of deep inspiration in lead III.

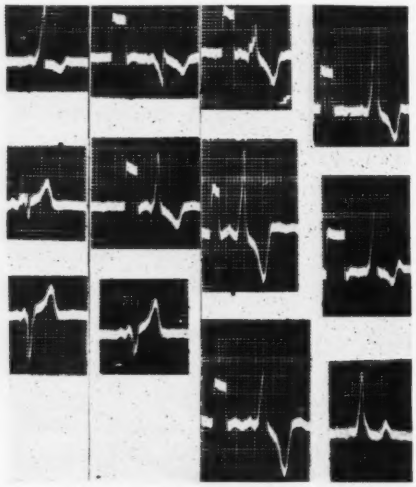

FIG. 8. Aircrew applicant, J. F. B., age 19. Routine tracing taken in October 1952, showed inverted T_2 and T_3. This repeat series taken three weeks later shows classic Wolff-Parkinson-White pattern.

revealed slight R-T or S-T deviation particularly in lead CF_4. These were considered to be of no significance with the possible exception of two instances, but repeat studies with a full set of leads were not considered to be indicative of significant abnormality, although some deviation of the segment persisted.

To sum up the T-wave findings: there were 88 subjects who revealed some defect in the T waves. On further examination seven of these continued to show significant abnormalities; five of these seven subjects also showed clinical findings suggestive of cardiovascular disorder which we felt were likely related to the electrocardiographic abnormality. All seven were therefore considered as unfit for aircrew training.

Prolonged QRS, Bundle Branch Block, and Wolff-Parkinson-White Syndrome

There were 28 subjects who showed prolongation of the QRS interval of 0.12 second or longer. Six of these 28 subjects revealed a classic Wolff-Parkinson-White syndrome (table 3) and on further clinical examination, three of the six revealed, cardiac findings suggestive of a possible cardiac disorder. These six subjects were considered as unsuitable for pilot training (figs. 8 and 9). In addition to the six subjects just discussed, four subjects showed P-R intervals of 0.12 second or less and QRS complexes of 0.12 second or more. While the Wolff-Parkinson-White syndrome was strongly suggested, the T waves were not abnormal and this diagnosis was not positively made (fig. 10). In one of these four subjects the repeat study was normal; in another, further clinical examination revealed the presence of mitral stenosis and aortic incompetence; the remaining two were passed as fit but were to be followed. Of the 10 subjects placed in the Wolff-Parkinson-White group there were, therefore, 7 considered to be unfit for pilot training.

There were 14 examples of bundle-branch block, 13 being right bundle-branch block. Seven of these subjects were considered to be unfit for pilot training. Five of the seven showed some associated clinical cardiovascular findings, such as top-normal heart size or systolic murmurs, which in the absence of the electrocardiographic findings would likely have been ignored. Two of these seven subjects were categorized as fit for aircrew positions other than pilot. Of the remaining seven

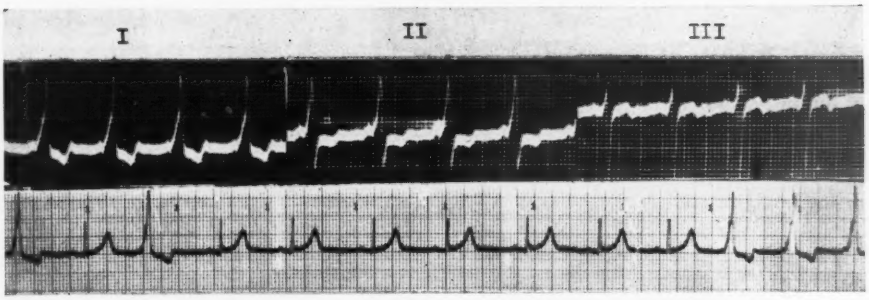

FIG. 9. D. J. M., age 23, not accepted for pilot training. Routine tracing showed classic Wolff-Parkinson-White. This repeat series taken November 1952, shows same findings with temporary change to normal conduction with subject in standing position. History of one "fainting spell." No other findings of significance from history or clinical examination. Blood pressure 106/70. Fluoroscopy normal.

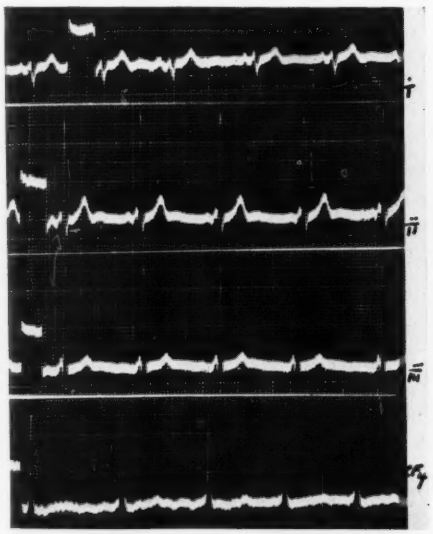

FIG. 10. Aircrew applicant, R. L. D., age 18. Routine tracing made in September 1952. Repeat studies showed same findings. History of chorea at age 7. Loud, split, first heart sound, accentuated second pulmonic sound and loud third heart sound, but no murmurs heard. Blood pressure 150/74. Fluoroscopy showed straight left border but otherwise normal.

subjects, four were not seen again and nothing further was done, one had a normal repeat study and was passed for training, and one showed the same findings on repeat study and was considered as fit for service. There was one subject in whom left bundle-branch block seemed to be shown in classic and unipolar limb leads but was not apparent in the precordial leads. This man was completely fit in all respects and was allowed to continue training, but was to be followed with repeat electrocardiographic studies.

There were four additional subjects with QRS complexes of 0.12 second in duration but no other abnormal findings. In three of these the QRS was within normal limits when repeat studies were carried out, and in one the duration remained the same. All four were considered fit.

In summary, then, of the 28 subjects in the group with prolonged QRS complexes, 12 were considered to be unfit for aircrew training, and an additional two subjects were categorized as fit for aircrew training other than pilot. Eight of these men showed some clinical evidence suggestive of cardiac abnormality which in the initial routine clinical examination had either been ignored or considered to be of such a minor degree as to be insignificant. In the presence of electrocardiographic abnormalities (learned of after the clinical examination) such findings, however, had to be considered in a different light.

Prolongation of the P-R Interval

There were 23 subjects whose electrocardiograms showed prolongation of the P-R interval of 0.24 second or more (table 4). In 14 of these subjects repeat studies showed either a normal P-R interval or one that could be brought into the normal range by assuming the upright

TABLE 3.—*Prolongation of QRS—28 Cases*

Classic W.P.W.	6
Borderline W.P.W.	4
R.B.B.B.	13
L.B.B.B.	1
QRS 0.12	4
UNFIT FOR PILOT TRAINING	
Basis of E.C.G. only 6	
Assoc. clinical findings 8	14

TABLE 4.—*Prolongation of P-R Interval—23 Cases*

Normal on repeat (posture)	14
Heart block	3
P-R 0.24–0.28	6
UNFIT FOR PILOT TRAINING	3

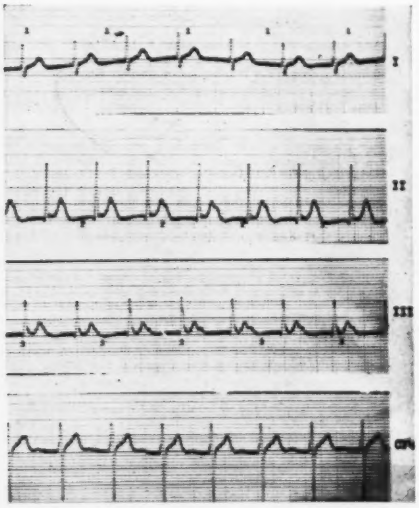

FIG. 11. J. D. V., age 20, considered unfit for pilot training. Tracing taken in May 1950 shows marked prolongation of P-R interval with P wave in preceding T wave. Reported to show no clinical cardiovascular abnormalities.

posture or by respiratory maneuvers. These subjects revealed nothing of significance on clinical examination of the heart. The P-R interval was never greater than 0.26 second and in the majority was approximately 0.24 second in the initial tracing. These 14 men were, therefore, considered to be normal and were passed as fit since normal findings were discovered when the repeat tracings were made. There were three additional subjects in this group who were considered to be unfit

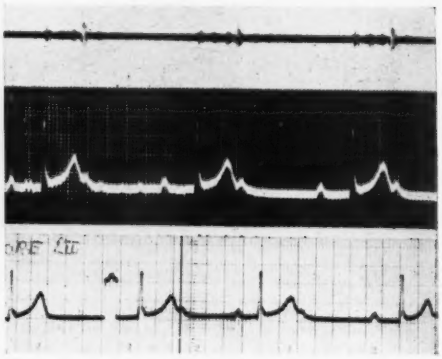

FIG. 12. N. H. M., age 19, not accepted for aircrew training. Routine tracing taken in September 1950 shows 2:1 A-V block. Heart sound tracing reveals soft first heart sounds, systolic murmur and auricular sound. Upper two tracings represent simultaneous lead III and heart sound tracing. Lower tracing shows another strip of lead II only. Other tracings revealed periodic complete heart block with a ventricular rate of 40.

for aircrew training following the discovery of definite heart block (figs. 11 and 12). There were six other subjects with the P-R interval ranging from 0.24 to 0.28 second in duration in whom repeat studies revealed the same conduction time. These subjects were passed as fit, since nothing could be found on clinical examination to suggest a cardiac disorder; they were to be followed throughout their service career. Eighteen months later, one of these men, while flying at approximately 3,000 feet in a jet fighter aircraft, crashed into a lake. Investigation of the accident suggested that he likely became disoriented due to low cloud formation. The cause of the crash, however, remains obscure since little or nothing of the aircraft or body was recovered. The electrocardiogram in this case showed a P-R interval of 0.28 second which could be reduced to normal by exercise. Moderately severe exercise (standing, running), however, simultaneously produced a definite change in the T wave of lead II (fig. 13). Although this fatal crash was probably unrelated to the heart of the pilot, its occurrence in such a case is somewhat disturbing.

To sum up: In the prolonged P-R group there were a total of 23 subjects, 14 of whom were considered to be normal on repeat study

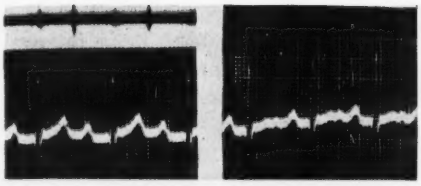

FIG. 13. R. W. R. age 18, a jet pilot, crashed into l:ke December 1953. Cause undetermined, but con-s:dered as likely pilot error. Lead II before (*left*) a:d after (*right*) exercise taken July 28, 1952.

TABLE 5.—*Miscellaneous Group—12 Cases*

Marked axis deviation	7
Deep Q in classic leads	2
Abnormality of rhythm	3
UNFIT FOR PILOT TRAINING	3

hypertrophy. One young man showed definite right ventricular hypertrophy in the electrocardiogram, a loud pulmonary second sound and cardiac enlargement on clinical examination. In view of the clinical findings as well as the routine and repeat electrocardiographic findings this man was considered to be unfit for aircrew training. The remaining six of the seven men referred to above showed little other than axis deviation, some of which could be attributed to cardiac rotation. They were considered to be fit for training but were to be followed.

Two of the 12 subjects showed deep Q waves, but in both of these a study of the limb and precordial leads appeared to explain

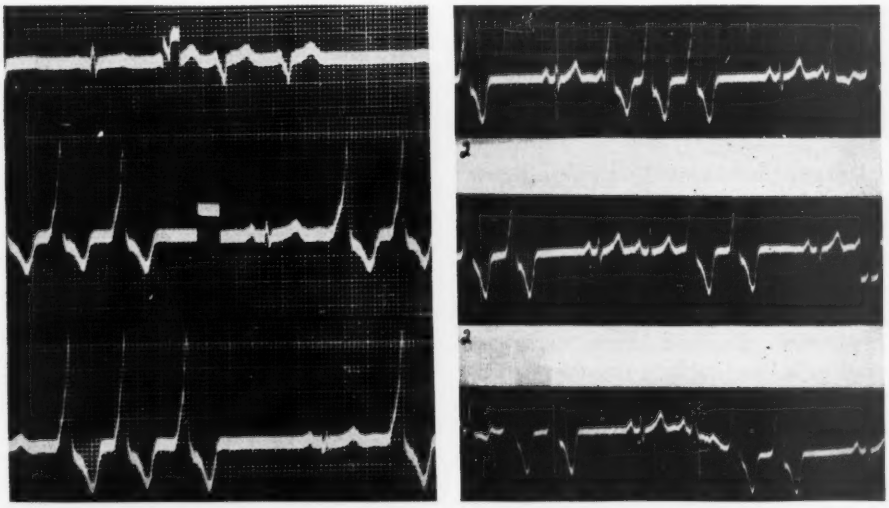

FIG. 14. L. R. W., age 22, not accepted for pilot training. *Left:* routine leads I, II, III taken in August 1952. *Right:* repeat studies (leads II) reveal similar findings with transition Wolff-Parkinson-White complexes initiating the runs of ventricular ectopic beats. No abnormal findings on clinical cardiovascular examination.

There were nine subjects who continued to reveal varying degrees of A-V block, three of whom were considered unfit for pilot training.

Miscellaneous Electrocardiographic Abnormalities

There were 12 subjects in this group. In seven, marked left or right axis deviation was the questionable findings (table 5). In some, the electrocardiograms were suggestive of the Q-wave abnormality, and these men were passed as fit since nothing could be found on repeat studies to suggest a cardiac disorder.

Three additional men showed abnormalities of rhythm. In one subject with tachycardia and right axis deviation, further electrocardiographic investigation confirmed the presence of paroxysmal auricular tachycardia with a ventricular rate of 160 per minute. Because of this he was rejected for pilot

training, but since the examination was in other respects normal, he was passed as fit for other aircrew duties. In another young man, frequent ventricular extrasystoles were noted in the initial tracing. In the repeat studies these occurred in runs of three (fig. 14). Although this man showed nothing of significance on clinical cardiovascular examination, the presence of frequent ventricular extrasystoles, at times occurring in short runs, rendered this man unfit for pilot training; however, he was passed as fit for training for other aircrew duties.

In summary then, in this group of 12 subjects with miscellaneous electrocardiographic abnormalities nine were accepted for pilot training; one man was considered to be unfit for any form of aircrew training following the discovery of right ventricular hypertrophy, and two others were accepted for training but only for aircrew duties other than pilot.

Discussion

In this study the routine electrocardiograms of 5,000 applicants between the ages of 18 and 24 for aircrew training with the Royal Canadian Air Force were reviewed. These men had passed the initial aircrew medical examination, which included x-ray study of the chest, and, on clinical grounds, were considered to be acceptable for flying training. One hundred and fifty eight applicants showed some abnormality in the initial electrocardiogram which suggested repeat study. Following further electrocardiographic and clinical studies, 27 or 5.4 per 1,000 were considered as unsuitable for pilot training: 15 of these 27 men showed some associated clinical cardiovascular findings in addition to the electrocardiographic abnormality. Four applicants were considered to be unfit for pilot training but were categorized as fit for aircrew training for duties other than that of pilot.

It is difficult to decide how much importance should be attached to an isolated electrocardiographic abnormality. If clinical evidence of some cardiac defect becomes apparent when the repeat studies are carried out, the decision, of course, is not difficult, for the candidate is then known to have some cardiac disorder which is probably responsible for the electrocardiographic abnormality. It is interesting to note that in 15 instances associated clinical cardiovascular findings were observed when repeat studies were carried out, which either had been overlooked or considered to be insignificant at the time of the initial medical examination. These men, however, would have been permitted to continue pilot training if routine electrocardiograms had not been taken immediately following the initial selection procedures.

Using this more rigid criteria (that is disqualifying only those who show some clinical finding in addition to the electrocardiographic variation) 3 per 1,000 or 0.3 per cent of those included in this study would have been considered to be unfit for pilot training. From the economic standpoint alone it is obvious that the elimination of even three physically unfit subjects out of 1,000 applicants makes the cost and trouble of obtaining 1,000 routine electrocardiograms a triviality. Apart from the economic aspects, of course, there are many other reasons both from military and civil considerations why medical selection at the present time must of necessity be most rigid. Since so few recruits show significant electrocardiographic abnormalities, there is no problem as far as the loss of manpower is concerned, and it would appear reasonable not to accept this group for aircrew training. On the other hand there are many who will say that an isolated electrocardiographic abnormality in the absence of any clinical findings should be disregarded. Although our follow-up evaluation of this small group with significant electrocardiographic abnormalities is by no means completed, a number of examples have occurred both in our own experience and in the experience of others to indicate that the chances of an organic cardiac disorder developing in this group is certainly far more likely than in the group showing rigidly normal electrocardiograms. Although an abnormal electrocardiogram may be the result of physiologic variation unassociated with heart disease, the chances are that it means something, particularly when one considers the very low incidence of significant abnormali-

ties in any large series of normal, healthy young men.

Long-term follow-up studies should of course answer the problem as to the significance of such findings. Since the incidence of significant abnormalities is so low, many thousand routine tracings have to be taken in order to obtain a sufficiently large group for follow-up purposes, and although the Royal Canadian Air Force has obtained many thousands it will take a number of years yet before significant information in this regard can be accumulated. If however, those with obvious electrocardiographic abnormalities are excluded from enlistment, not only will the follow-up become more difficult, but we will not have the opportunity to follow such cases under the added stress and strain of military flying. Considering everything, however, it is not feasible to train such candidates, particularly as pilots. If a routine electrocardiogram is recorded in all aircrew prior to flying training then the occurrence of an abnormality in a later tracing will have much greater significance than the finding of an isolated electrocardiographic abnormality.

In some instances training for other aircrew duties than those of pilot might be considered. However, although the responsibility of the crewman is not as great as that of the pilot, the financial aspect is still a large factor and consequently one perhaps should consider such cases somewhat in the light of the insurance underwriter in evaluating the acceptability of a client for a policy of the same order.

Unfortunately we are not in possession of sufficient information at the present time to state with any degree of accuracy the prognosis in any particular electrocardiographic abnormality occurring in an otherwise fit individual. Packard, Grettinger and Graybiel[10] have recently reported a 10 year follow-up study on 1,000 United States Army Air Force aviators. Here again relatively few (nine) abnormal electrocardiograms were encountered, and at the end of 10 years no cardiovascular disease had occurred in those from whom these electrocardiograms were obtained. Mathewson has reported[11] the favorable course in men showing prolongation of the P-R interval. Others have reported on the favorable course in certain electrocardiographic abnormalities occurring in the absence of any significant clinical cardiovascular findings. On the other hand electrocardiographic abnormalities occurring in routine surveys have led us (on further cardiovascular investigation) to the discovery of clinical cardiovascular abnormalities (0.3 per cent). Furthermore a number of examples of the Wolff-Parkinson-White syndrome have been shown to be associated with significant heart disease which has at times produced sudden death[7]. In our own earlier experience abnormal electrocardiographic findings in a few instances have been followed by significant cardiac disorders (sudden death in two cases). Paroxysmal auricular tachycardia or fibrillation, frequent extrasystoles, and other abnormalities of rhythm may not be of significance or importance as far as the outlook for a civilian subject is concerned but could well be of considerable importance to those responsible for an aircraft, particularly in the field of military aviation.

Considering everything the procedure of obtaining a routine electrocardiogram on all seeking to enlist is practical; those with significant abnormalities should not be accepted for flying training.

The present policy of the Royal Canadian Air Force is to record routinely six leads (I, II, III, V_2, V_4, V_6) on all aircrew applicants before enlistment, and subsequently to record 12 leads (I, II, III, aV_R, aV_L, aV_F, V_1 to V_6) in all questionable cases. If selection alone was the only consideration fewer leads might suffice. In fact lead I alone might prove to be of sufficient value from this standpoint. If, however, any tracing is to be obtained, the cost in time and money of recording multiple leads is trivial when compared with the value of a complete tracing for follow-up studies and for comparison with future tracings when the possibility of a cardiac disorder arises.

Summary

1. Routine electrocardiograms of 5,000 apparently healthy, fit Royal Canadian Air

Force aircrew applicants, between the ages of 18 and 24 years have been reviewed.

2. Possibly significant abnormalities were observed in 158 young men who were recalled for further study.

3. T-wave abnormalities occurred in 95 subjects, prolongation of QRS (including Wolff-Parkinson-White syndrome) in 28, prolongation of P-R interval in 23, and additional miscellaneous electrocardiographic changes in 12 applicants.

4. Twenty-seven of the entire group were considered to be unfit for pilot training (0.54 per cent). Fifteen of these 27 men showed some associated clinical cardiovascular findings.

Sumario Español

1. Electrocardiogramas rutinarios de 5,000 candidatos aparentemente saludables para tripulaciones de la Real Fuerza Aerea Canadiense, entre las edades de 18 a 24 años han sido revisados.

2. Posiblemente anormalidades significativas fueron observadas en 158 hombres jovenes que fueron llamados para subsiguientes estudios.

3. Anormalidades de la onda T ocurrieron en 95 sujetos, prolongación de QRS (incluyendo el síndrome de Wolff-Parkinson White) en 28, prolongación del intervalo P-R en 23, y cambios adicionales misceláneos en 12 candidatos.

4. Veinte y siete del grupo entero fueron considerados ineptos para entrenamiento como pilotos (0.54 por ciento). Quince de estos 27 hombres mostraron algunos hallazgos clínicos cardiovasculares.

Acknowledgment

The author wishes to thank the Department of Transport (Canada) for permission to use the electrocardiogram shown in figure 2.

The co-operation and assistance of the medical and technical staff of No. 1 Medical Selection Unit, Royal Canadian Air Force Station, London, is most gratefully acknowledged.

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Postural Hypotension Induced by Atropine Sulfate

By MARTIN H. KALSER, M.D., PH.D., CHARLES W. FRYE, M.S., AND ARCHER S. GORDON, M.D., PH.D.

Previous tests on the use of large doses of atropine for the treatment of anticholinesterase poisoning have revealed postural hypotension following the administration of 2 mg. of this drug. In this study on 78 normal adult males, the cardiovascular responses to positional change after 2 mg. atropine have been measured and the mechanisms elucidated. Blood pressure response to tilting was normal during control and placebo phases, but showed a profound alteration after atropine.

THE recommended therapy for anticholinesterase intoxication is atropine sulfate and artificial respiration.[1] The use of anticholinesterases as insecticides and their potential use as chemical warfare nerve gas agents has rekindled an interest in this well-known parasympatholytic drug and the manual methods of resuscitation.

Atropine sulfate has found a wide range of clinical applications. In most instances it is prescribed in small doses (0.3 mg. to 0.6 mg.). However, it has been established that human tolerance to this drug in the presence of anticholinesterase agents is enormous.[2] Its immediate injection in case of exposure is imperative, and the recommended initial dose is 2 mg.

In civil defense emergencies and possible insecticide exposures, it may become necessary to administer this large dose of atropine to normal, but potentially poisoned, individuals. This possibility has made it desirable to determine the physiologic effects resulting in normal individuals from the intramuscular injection of 2 mg. of atropine sulfate.

Previous reports have detailed the muscular, visual and psychologic effects of doses of atropine up to 3 mg.[3] In a study conducted by this group on 200 normal college men,[4] no serious signs or symptoms were noted following the administration of the recommended initial intramuscular dose. However, hypotension and vertigo were observed in some individuals while they were standing. Accordingly, it seemed appropriate to investigate specific cardiovascular responses of normal adults to the intramuscular injection of 2 mg. of atropine sulfate. In the current study the phenomenon of atropine-induced postural hypotension has been carefully assayed along with an attempt to determine the mechanism of this action.

METHODS

The experimental procedure consisted of three phases carried out on a series of 73 normal male military subjects,* who were in a random height and weight range and whose average age was under 25 years.

In the first (control) phase, blood pressure, pulse rate, and temperature were recorded before any injection was given. During the second (placebo) phase these same measurements were made from 50 to 70 minutes after a placebo of 1 cc. normal saline was administered intramuscularly. In the third (atropine) phase, determinations were made from 50 to 70 minutes after each subject had received the intramuscular injection of 2 mg. of atropine sulfate in 1 cc. of isotonic physiologically inactive solution.

For the major group of 58 men, the three phases of the study were performed on each individual in the sequence listed above. Each phase included a 10-minute recumbent period immediately followed by a 10-minute period during which the subjects stood "at attention." Active rather than passive change of position was used because it was felt that this would provide a more physiologic test of orthostatic hypotension. In a second group of 15 men, the control phase was omitted and a second 20-minute period was used in both the placebo and atropine

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phases to evaluate the effect of exercise during the standing period.

Determinations of blood pressure, pulse rate and skin and oral temperature were made at frequent regular intervals during these periods. Blood pressure was measured by auscultation and heart rate by counting the radial pulse for 30 seconds. An oral thermometer was used to determine body temperature, while skin temperature was measured with a 0 to 100 C. laboratory thermometer held by the subject between his thumb and index finger. The experiments were all completed within three days during the Spring, and the ambient temperature ranged from 72 F. to 84 F., with an average relative humidity of 60 per cent. Both the placebo and the atropine sulfate were given intramuscularly from identical type Ampins.*

Following the placebo phase, all subjects were asked to complete a standard questionnaire† listing possible symptoms. A similar questionnaire was given to the subjects at the end of the atropine phase.

Results

Symptoms (table 1). Approximately 6 per cent of the subjects experienced various symptoms after the injection of the placebo. This group serves to distinguish the psychic effects of the injection, per se, from the pharmacologic effects of the atropine. Following the 2 mg. dose of atropine sulfate, the major symptoms were dryness of mucosal surfaces, visual disturbances, vertigo, flushing and fatigue. Other symptoms included palpitation and paresthesias. Although these symptoms were frequent, in no instance were they found to be more than mildly annoying. Specific psychomotor performance tests were not done, but all subjects were able to cooperate comfortably throughout the studies and returned to their routine activities immediately thereafter.

Oral Temperature. The mean oral temperature in all 73 individuals prior to the injections was 98.6 F., while after the injection the average body temperature was 98.3 F. Although the average fall is only 0.3 degrees, this change in body temperature is statistically significant. A fall in postatropine body temperature occurred in 49 subjects, an elevation in 12 and no change in 12. The probability that so many individuals would show a drop in body temperature by chance alone is less than 0.001.

Skin Temperature. The mean skin temperature of the hand in the same 73 subjects prior to atropine was 34.9 C. (94.8 F.), while after the injection it increased to 36.1 C. (97.0 F.). This increase was statistically significant and was noted in 60 subjects while a decrease was seen in four and the remaining nine showed no change.

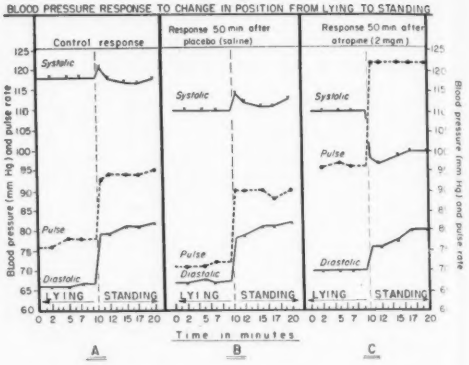

FIG. 1. Comparison of blood pressure and pulse rate response of 48 normal adult males with change in position from lying to standing during (*A*) control Phase, (*B*) placebo Phase, and (*C*) atropine Phase, following 2 mg. of atropine sulfate.

TABLE 1.—*Symptoms Reported by 73 Normal Adult Males Following Placebo and 2 mg. Atropine Sulfate Intramuscularly*

Symptom	Placebo (%)	Atropine (%)
1. Dryness	5.8	78.2
2. Vertigo	5.8	31.9
3. Tired	8.7	34.8
4. Eye Trouble	2.9	30.4
5. Flushing	5.8	30.4
6. Palpitation	1.4	11.6
7. Paresthesias	4.3	11.6
8. Headache	1.4	5.8

97% Reported greater effects from second injection (atropine)
3% Reported no difference between the two injections.

* Standard Ampins containing 2 mg. of atropine sulfate in 1 cc. of isotonic physiologically inactive solution, and Placebo Ampins containing 1 cc. of isotonic physiologically inactive solution, manufactured by Strong Cobb Co., Cleveland, were furnished by Army Chemical Corps Medical Laboratories.

† Questionnaires were prepared by Dr. Shirley Star and Mr. Frederic Meier, National Opinion Research Center, Chicago, Ill., with careful attention to elimination of suggestion and bias.

Blood Pressure (fig. 1 and table 2). A characteristic blood pressure reaction to positional change was noted in the control and placebo phases. In both, the systolic pressure rose 4 mm. Hg immediately after standing and then fell to control levels during the remainder of the erect period. The mean diastolic pressure during the control and placebo phases rose 12 and 10 mm. Hg, respectively, immediately after change of position and increased slightly thereafter. Following atropine, however, the mean blood pressure response to postural change was markedly altered. The systolic pressure, instead of increasing, immediately fell 11 mm. Hg and then increased slightly during the following 10 minutes. The immediate diastolic response was an increase of 5 mm. Hg which was only one-half of the rise seen in the preceding phases. During the 10-minute erect period, the diastolic pressure continued to rise so that the final increase approached that of the control and placebo phases, indicating a delayed diastolic response.*

Pulse Rate (fig. 1 and table 2). The mean pulse rate following the placebo was 72 per minute during the supine period and 90 per minute following standing. During the atropine phase, it was 97 and 122 per minute, respectively, in the supine and erect periods. Except for the initial elevation in pulse rate resulting from the atropine, the reaction to change of position was similar in both phases.*

Syncope (fig. 2 and tables 3A and 3B). Ten of the 58 subjects for whom three phases were determined developed syncope when they stood after receiving 2 mg. of atropine. Accordingly, they have been considered as a separate group as far as blood pressure and pulse rate data are concerned and have not been included in the above results. Their pulse and blood pressure responses to positional change following the placebo were similar to the responses of the previous group. However, following atropine, syncope developed in each of these cases either immediately or within seven minutes after standing. In evaluation of this data, the last obtainable pulse rate and blood pressure preceding the onset of syncope were recorded for each subject. The average of these last blood pressures immediately preceding syncope was 84/65 and the average pulse rate was 116 beats per minute.

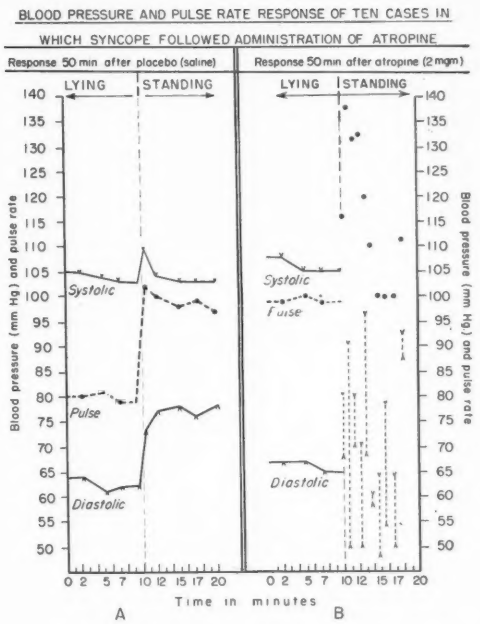

FIG. 2. Comparison of blood pressure and pulse rate response with change in position from lying to standing in 10 essentially normal adult males who gave (*A*) normal response following placebo, but (*B*) developed syncope following administration of 2 mg. of atropine sulfate.

During standing period following atropine the last obtainable pulse (solid dots) and blood pressure (broken vertical lines) before syncope are noted for each individual case. Mean values for last obtainable pulse, 116; last obtainable blood pressure, 84/65.

Normal, Abnormal and Syncope Responses (table 4). By a modification of the criteria of Eichna, Horvath and Bean,[5] blood pressure response to postural change can be classified into three groups on the basis of systolic blood pressure after standing. (1) The normal response shows erect systolic blood pressures above 100 mm. Hg. (2) An abnormal response is characterized by (a) any erect systolic pressure below 100 mm. Hg, and (b) a fall of at least 10 mm. Hg from the lowest supine pressure. (3) The third group includes all cases

* The differences in response which have been described are statistically significant.

TABLE 2.—*Mean and Range of Temperature, Pulse and Blood Pressure Response of 48 Normal Adult Males Following Change in Position from Lying to Standing During Control, Placebo and Atropine Phases*

Measurement	Control Phase		Placebo Phase		Atropine Phase	
Oral Temperature (°F.)						
Lying	98.5 (97.0–99.2)		98.4 (97.0–99.6)		98.3 (96.8–99.8)	
Standing	98.7 (97.0–99.8)		98.5 (97.8–99.6)		98.4 (97.0–99.6)	
Skin Temperature (°C.)						
Lying	34.7 (28–38)		35.7 (33–37)		36.3 (35–38)	
Standing	35.1 (28–38)		35.6 (33–37)		36.3 (34–38)	
Pulse						
Lying:						
2 minutes	76 (52–100)		72 (48–100)		96 (50–126)	
5 minutes	78 (54–104)		72 (48–100)		97 (50–128)	
7 minutes	78 (54–100)		72 (48–100)		97 (56–126)	
Standing:						
10 minutes	93 (70–118)		91 (64–122)		122 (80–166)	
12 minutes	94 (68–112)		90 (66–116)		122 (84–164)	
15 minutes	93 (66–122)		90 (62–120)		122 (82–162)	
17 minutes	94 (68–118)		87 (68–118)		121 (84–160)	
20 minutes	95 (62–118)		89 (66–118)		122 (88–158)	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Blood Pressure						
Lying:						
2 minutes	118 (102–138)	66 (38–82)	109 (90–130)	67 (50–86)	111 (94–126)	71 (38–90)
5 minutes	117 (98–142)	66 (36–86)	108 (90–128)	68 (50–86)	109 (80–130)	70 (40–90)
7 minutes	116 (98–144)	67 (44–86)	108 (90–130)	67 (50–86)	109 (88–132)	70 (38–90)
Standing:						
10 minutes (after exercise)	120 (94–160)	79 (60–104)	112 (96–140)	77 (40–98)	98 (80–128)	75 (52–99)
12 minutes	117 (98–140)	80 (64–98)	110 (86–160)	78 (60–98)	97 (70–132)	77 (54–99)
15 minutes	116 (96–142)	81 (64–104)	109 (88–148)	80 (60–98)	100 (80–128)	79 (56–104)
17 minutes	116 (96–150)	81 (64–112)	108 (80–148)	81 (64–98)	100 (80–128)	81 (60–104)
20 minutes	118 (90–144)	81 (62–110)	109 (82–146)	83 (66–108)	102 (84–128)	80 (62–94)

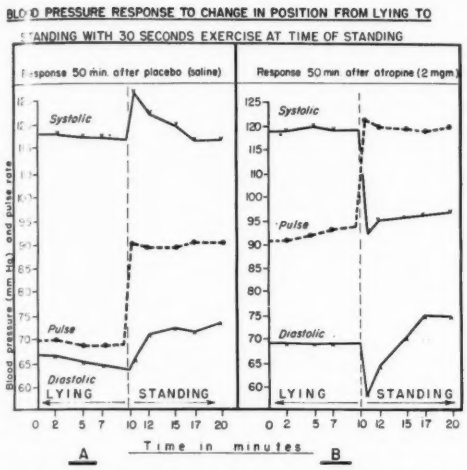
BLOOD PRESSURE RESPONSE TO CHANGE IN POSITION FROM LYING TO STANDING WITH 30 SECONDS EXERCISE AT TIME OF STANDING
Response 50 min. after placebo (saline)
Response 50 mn. after atropine (2 mgm.)
Systolic
Pulse
Diastolic
LYING
STANDING
Blood pressure (mm Hg) and pulse rate
Time in minutes
A
B

FIG. 3. Comparison of blood pressure and pulse rate response of 15 normal adult males associated with change in position from lying to standing with 30 seconds standard exercise at time of standing, following: (*A*) placebo, and (*B*) atropine sulfate, 2 mg.

that develop syncope. Using this classification, 95 per cent of our subjects had a normal reaction in the control and placebo phases, while after atropine less than one-half had normal reactions and 12.5 per cent developed syncope.

Effect of Exercise (fig. 3 and table 5). In the group of 15 subjects, the circulatory effects of a standard exercise were compared after the injection of the placebo and the atropine. The standard exercise consisted of stepping on and off a 14-inch vertical elevation 15 times in 30 seconds immediately after standing, and then remaining standing for 10 minutes.

In this series, the normal response when the erect position was maintained following the standard exercise was an immediate transient increase of the systolic pressure which then returned to normal. The diastolic pressure increased 2 mm. Hg immediately after exercise and continued to rise slowly during the remainder of the 10-minute standing period.

The effect of atropine on the blood pressure response after exercise was a remarkable alteration of this pattern. While standing, immediately after exercise, the mean systolic pressure fell 22 mm. Hg and remained at this low level. Simultaneously, the diastolic pressure fell 12 mm. Hg, but gradually increased during the following 10 minutes to a reading slightly above preexercise levels, the final result being a decrease in the pulse pressure.

DISCUSSION

The normal physiologic response to a change from the horizontal to the vertical stance consists of an initial fall in systolic blood pressure lasting several seconds. This stimulates the carotid sinus and related reflex mechanisms mediated by the autonomic nervous system, with resultant increase in arterial blood pressure and acceleration of the heart.[6]

Orthostatic hypotension occurs in individuals in whom these reflex mechanisms are hyposensitive and fail to initiate the compensatory blood pressure rise. Various studies have shown that the stress of exhausting exercise, prolonged work or hot baths can accentuate this phenomenon and result in postural hypotension in a significant number of otherwise normal subjects.[7] In the latter experiments, peripheral pooling and inadequate venous return were believed to be the principal factors responsible for the failure of normal blood pressure reaction in the erect position.

The current study confirms our previous observations[4] that 2 mg of atropine fails to produce serious signs or symptoms in normal adult males, but that an alteration in blood pressure response occurs with change from the supine to the vertical position. It shows further that this effect is enhanced by exercise. An explanation of the exact mechanism of this orthostatic hypotension cannot be made on the basis of either these studies or the usually accepted muscarinic blocking action of atropine. However, there are several other possible hypotheses which will be discussed.

1. With severe tachycardia, decreased ventricular filling can occur as a consequence of significant shortening of diastole, but this does not interfere with cardiac output until the heart rate is at least 180 per minute.[8] In our cases, even where syncope occurred after atropine, the average heart rate just prior to collapse was 116 per minute. Thus, it would appear that the atropine-induced tachycardia,

TABLE 3A.—*Mean and Range of Temperature, Pulse and Blood Pressure Response Following Change in Position from Lying to Standing, during Control, Placebo and Atropine Phases in 10 Normal Adult Males in Whom Syncope Developed Following the Administration of 2 mg. Atropine Sulfate*

Measurement	Control Phase		Placebo Phase		Atropine Phase	
Oral Temperature (°F.)						
Lying	98.7 (97.4–99.4)		98.6 (97.6–99.0)		98.5 (97.0–99.4)	
Standing	98.8 (97.6–99.8)		98.7 (97.4–99.4)		98.6 (97.4–99.6)	
Skin Temperature (°C.)						
Lying	35.8 (33–37)		36.1 (34–37)		36.8 (36–37)	
Standing	35.8 (33–37)		36.2 (34–37)		36.8 (36–37)	
Pulse						
Lying:						
2 minutes	72 (60–96)		80 (62–108)		98 (84–120)	
5 minutes	73 (56–96)		82 (62–108)		100 (82–120)	
7 minutes	73 (60–94)		79 (62–102)		98 (86–124)	
Standing:						
10 minutes	93 (72–108)		103 (74–120)		*	
12 minutes	99 (78–116)		102 (76–120)			
15 minutes	94 (72–112)		99 (70–120)			
17 minutes	94 (74–116)		100 (72–122)			
20 minutes	93 (76–120)		98 (80–116)			
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Blood Pressure						
Lying:						
2 minutes	112 (94–134)	55 (30–70)	105 (96–120)	63 (50–76)	108 (100–114)	67 (50–80)
5 minutes	112 (94–130)	58 (34–72)	105 (96–116)	60 (40–78)	106 (90–120)	65 (20–78)
7 minutes	111 (92–130)	58 (34–70)	103 (90–118)	61 (44–76)	106 (100–116)	64 (40–80)
Standing:						
10 minutes (after exercise)	107 (96–136)	70 (58–80)	109 (80–118)	74 (70–86)	*	*
12 minutes	107 (86–132)	70 (50–84)	105 (90–116)	79 (68–92)		
15 minutes	107 (90–128)	73 (64–80)	104 (90–118)	78 (66–92)		
17 minutes	106 (90–128)	73 (66–80)	104 (96–118)	76 (66–94)		
20 minutes	105 (80–128)	74 (60–84)	104 (96–122)	79 (70–92)		

* See figure 2 and table 3*B* for individual data.

TABLE 3B.*—*Blood Pressure and Pulse Records of Ten Individuals Who Developed Syncope after Standing Following 2 mg. Atropine Sulfate Intramuscularly*

Case No.	Standing Blood Pressure					Standing Pulse				
	minutes					minutes				
	10	12	15	17	20	10	12	15	17	20
74	80/68	—	—	—	—	116	—	—	—	—
71	90/50	—	—	—	—	138	—	—	—	—
28	90/72	80/70	—	—	—	124	132	—	—	—
69	90/50	70/50	—	—	—	118	132	—	—	—
32	108/68	100/68	98/68	—	—	100	116	120	—	—
37	88/76	72/64	60/58	—	—	128	134	110	—	—
51	76/50	68/50	64/48	—	—	98	102	100	—	—
73	108/70	84/54	78/54	—	—	104	98	100	—	—
72	98/72	96/68	80/60	64/50	—	108	106	110	100	—
62	118/98	90/80	100/90	92/88	—	104	102	108	112	—

* For mean values of all cases during placebo phase refer to table 3A. Mean of last obtainable pulse rate, 116; mean of last obtainable blood pressure, 84/65.

TABLE 4.—*Summary of Systolic Blood Pressure Response to Change in Position from Lying to Standing*

Phase	Response		
	Normal*	Abnormal†	Syncope‡
Control.....	93.8%	4.2%	2.0%
Placebo.....	96.9%	3.1%	0.0%
Atropine	45.8%	41.7%	12.5%

* Systolic blood pressure above 100 mm. Hg while standing.

† (a) Systolic blood pressure below 100 mm. Hg, and (b) at least 10 mm. Hg fall below lowest control level while standing.

‡ Cases who developed signs and symptoms of collapse with fainting, while standing.

per se, was not responsible for the low blood pressure.

2. Another possible explanation would be an alteration of the normal pressor response to standing resulting from vasodilatation and impaired venous return. Several factors tend to indicate that vasodilatation did occur in these subjects after atropine administration. First, a significant elevation of skin temperature occurred, while body temperature decreased. Also, in those subjects who developed syncope while standing, marked elevation of the systolic and diastolic pressure above their initial levels occurred immediately after lying down. This indicates that with resumption of the supine position, the circulating blood volume increased rapidly as a result of the return of pooled blood to the general circulation.

Vasodilatation of the superficial vessels of the face and neck, the "atropine flush," is well-known, but the mechanism of this cutaneous phenomenen remains controversial. Whether dilatation of cutaneous vessels alone could divert sufficient blood from the effective circulating volume to result in postural hypotension is uncertain. However, it appears improbable that this superficial reservoir can be held responsible for the production of profound hypotension and syncope. The large dependent muscle masses of the extremities and/or the splanchnic bed offer more probable sites for the occurrence of vascular pooling resulting in orthostatic hypotension following 2 mg. of atropine sulfate. Carefully controlled studies have been carried out to support this view and are reported elsewhere.[9]

Although vascular pooling may be incriminated as the mechanism resulting in atropine-induced postural hypotension, the exact mechanism responsible for the pooling remains equivocal. Previous investigators have alternately attributed vascular relaxation following atropine to central depression, ganglionic blockade or terminal action. Although atropine is usually credited only with the role of muscarinic blockade, the studies of Marrazzi[10, 11]

TABLE 5.—*Mean and Range of Temperature, Pulse and Blood Pressure Response of 15 Normal Adult Males, Following Change in Position from Lying to Standing, and with Exercise upon Standing, during Placebo and Atropine Phases*

Measurement	Placebo Phase		Atropine Phase	
Oral Temperature (°F.)				
Lying	98.6 (97.8–99.8)		98.3 (97.4–99.4)	
Standing	98.7 (97.8–100.0)		98.4 (96.6–99.4)	
Skin Temperature (°C.)				
Lying	33.3 (26–37)		35.1 (32–37)	
Standing	32.7 (26–36)		34.9 (31–37)	
Pulse				
Lying:				
2 minutes	69 (56–98)		91 (62–130)	
5 minutes	68 (54–96)		93 (66–126)	
7 minutes	68 (56–98)		94 (76–120)	
Standing:				
10 minutes	91 (74–124)		122 (94–156)	
12 minutes	90 (68–124)		120 (94–154)	
15 minutes	90 (68–122)		119 (92–150)	
17 minutes	91 (66–118)		118 (90–148)	
20 minutes	91 (66–120)		119 (90–148)	
	Systolic	Diastolic	Systolic	Diastolic
Blood Pressure				
Lying:				
2 minutes	118 (102–136)	67 (58–86)	118 (104–138)	68 (56–92)
5 minutes	117 (102–130)	66 (56–86)	120 (106–142)	67 (58–99)
7 minutes	117 (102–130)	65 (58–84)	118 (102–144)	68 (58–98)
Standing:				
10 minutes (after exercise)	127 (100–152)	67 (52–90)	93 (90–144)	58 (50–98)
12 minutes	123 (100–138)	72 (64–99)	95 (94–140)	63 (50–99)
15 minutes	120 (100–134)	73 (60–94)	96 (90–138)	70 (57–99)
17 minutes	118 (100–134)	72 (60–88)	97 (72–126)	75 (61–99)
20 minutes	119 (100–134)	74 (62–92)	97 (88–128)	74 (64–99)

have attributed a ganglionic blocking action to the drug. It is of interest in this regard that the studies of Brown and coworkers[12] with a known ganglionic blocking agent, tetraethylammonium chloride, revealed an orthostatic hypotension similar in severity to that observed in the current study. Sollman[13] mentions Regnier's work indicating that large doses of atropine antagonize the constrictor action of epinephrine. Gyermek[14] noted a lowering of blood pressure in cats following the administration of atropine, and states that it is due to ganglionic blockade but that this depends upon the sympathetic vasomotor tonus of the animal. Other investigators[15] have used atropine to abolish the vasoconstriction induced by adrenaline or sympathetic nerve stimulation in the vessels of the rabbit's ear.

Salter[16] mentions that large doses of atropine depress the central vasoconstrictor center with loss of vascular tone. He further cites the studies and review of Hamet[17] on the effects of atropine directly at the peripheral level in causing relaxation of vascular smooth muscle.

The development of postural hypotension in human subjects following the administration of 2 mg. of atropine and, apparently, due to pooling in the splanchnic and dependent areas, appears well substantiated. However, conflicting evidence precludes assigning the mechanism to a central, ganglionic or terminal blockade of sympathetic vasoconstrictor tone, or combination of these factors.

Conclusions

1. Studies performed on 78 normal adult males reveal that no serious symptoms or physiologic effects result from the intramuscular injection of 2 mg. of atropine sulfate, which is the recommended initial dose following exposure to the anticholinesterase nerve gas agents or insecticides.

2. These subjects have been observed to exhibit a normal blood pressure and pulse rate response to change in position from supine to erect in control studies and following a placebo of 1 cc. of an isotonic physiologically inactive solution. This consisted of a slight rise in systolic pressure, with a gradual return to normal, and a marked rise in pulse rate and diastolic pressure with the elevation being sustained or increasing slightly.

3. Following atropine this normal blood pressure response was altered and was characterized by a profound and sustained fall in systolic pressure with only one-half the previous diastolic rise.

4. A 30-second period of standard exercise at the time of standing enhanced this fall in systolic pressure and resulted in a simultaneous fall in diastolic pressure.

Sumario Español

1. Estudios efectuados en 78 adultos varones normales revelaron que luego de la inyección intramuscular de 2 mg. de sulfato de atropina que es la dosis inicial recomendada después de la exposición a agentes de gas anti-colinesterasa nerviosos o insecticidas, no ocurrieron síntomas o efectos fisiológicos serios.

2. Estos sujetos se han observado exhibir una presión arterial normal y pulso como respuesta al cambio en posición de la posición acostada a la erecta en estudios controles y luego de la administración de placebo de 1 cc. de solución isotónica fisiologicamente inactiva. Esto consistió en un ligero aumento en presión sistólica, con un retorno gradual a lo normal y un marcado aumento en el pulso y la presión diastólica con la elevación siendo sostenida o aumentando gradualmente.

3. Luego de la atropina esta respuesta normal de la presión arterial fué alterada y se caracterizó por una profunda y sostenida caída en presión sistólica con solamente la mitad del previo incremento diastólico.

4. Un período de ejercicio uniforme al tiempo de asumir la posición erecta favoreció la caída en presión sistólica y resultó en una caída simultánea en la presión diastólica.

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Measurement of Atropine-Induced Vascular Pooling

By Robert D. Miller, M.A., Martin H. Kalser, M.D., Ph.D., Charles W. Frye, M.S., and Archer S. Gordon, M.D., Ph.D.

Postural hypotension resulting from 2 mg. of intramuscular atropine appears to be due to peripheral vascular pooling. Controlled studies on 31 normal adult males are reported here and reveal that external compression of the abdomen and lower extremities allows partial cardiovascular compensation. Simultaneous compression of both legs and abdomen is even more effective in preventing postural hypotension. The effects of 2 mg. of atropine appear to be due to partial vagal block, partial ganglionic block and central excitation.

THE studies of Gordon and his coworkers,[1] and Kalser and associates[2] have demonstrated the development of postural hypotension in a significant number of healthy, young adult males following the intramuscular injection of 2 mg. of atropine sulfate. The most probable explanation for this phenomenon appeared to be vascular pooling in dependent muscle masses and/or the splanchnic bed. The present investigation was undertaken to assess the role of this mechanism in the production of atropine-induced postural hypotension.

Experimental Design

Thirty-one normal adult males were carefully evaluated following the intramuscular injection of 2 mg. of atropine sulfate and comparison was made with similar evaluations following a control injection of isotonic physiologically inactive solution. Twenty of these subjects were studied as regards the effects of vascular pooling on the response to tilting from the horizontal to vertical position.

Each subject, shoeless and dressed in an antiblackout suit,* was placed supine on a tilt table equipped with a foot board and was given 1 cc. of an isotonic physiologically inactive solution. He then rested for 35 minutes, after which blood pressure and pulse were recorded frequently during four successive test periods of 10 minutes each. Each test period was divided into two five-minute phases. The first phase was in the horizontal position and was followed by tilting to 80 degrees and maintenance for five minutes in the vertical position.

At each tilt to the vertical some variant of inflation of the antiblackout suit was instituted during each test period. These included: (1) no inflation of the suit; (2) inflation of the abdominal compartment only; (3) inflation of the lower extremities compartment only; and (4) total inflation of both the abdominal and lower extremities compartments simultaneously. The sequence of inflation was varied between subjects at calculated random. A pressure of 3 pounds per square inch was used to compress the abdomen and lower limbs. This pressure did not occlude the dorsalis pedis pulse nor cause any swelling of the feet.

Immediately after completion of the four test periods with the placebo, each subject was injected intramuscularly with 2 mg. of atropine sulfate in isotonic physiologically inactive solution. The entire procedure was then repeated, the sequence of application of pressure being the same for each subject as during the placebo tests. The subjects were instructed to lie and stand relaxed, but without moving, at all times during the testing.

Blood pressure was recorded by auscultation except when it could not be heard, in which case it was determined by palpation at the radial artery. Pulse was checked at the radial artery for 30-second intervals.

The room was quiet and maintained at a temperature between 70 and 75 F. Placebo and atropine injections were standardized by administration from identical type Ampins.*

Results

Blood Pressure. This dosage of atropine sulfate resulted in a significant alteration of the arterial blood pressure from the placebo response of the 20 subjects.

Following the placebo injection, when no pressure was applied, the diastolic pressure

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* Suit manufactured by Pioneer Product Division, General Electric Co., and supplied to the investigators by Wright-Patterson Air Force Base, Dayton, Ohio.

* Ampins manufactured by Strong Cobb and Company, Inc., Cleveland, Ohio.

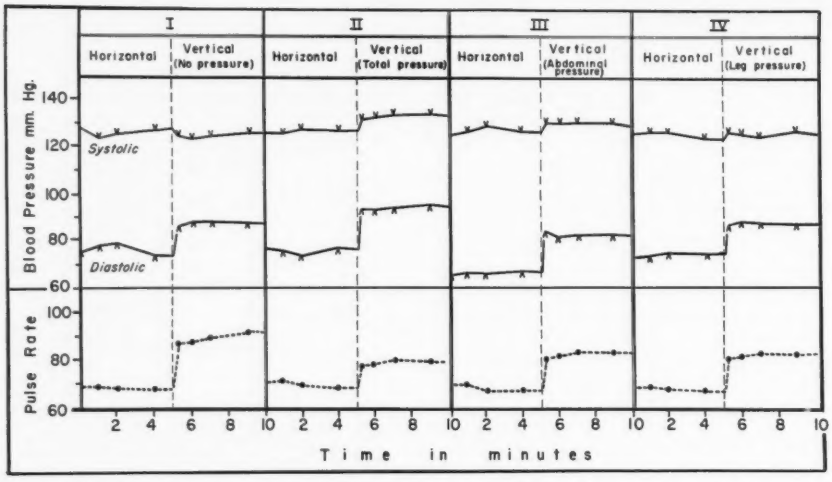

FIG. 1. Circulatory response to change in position from horizontal to vertical following intramuscular placebo or normal saline. Mean response of 20 normal adult males.

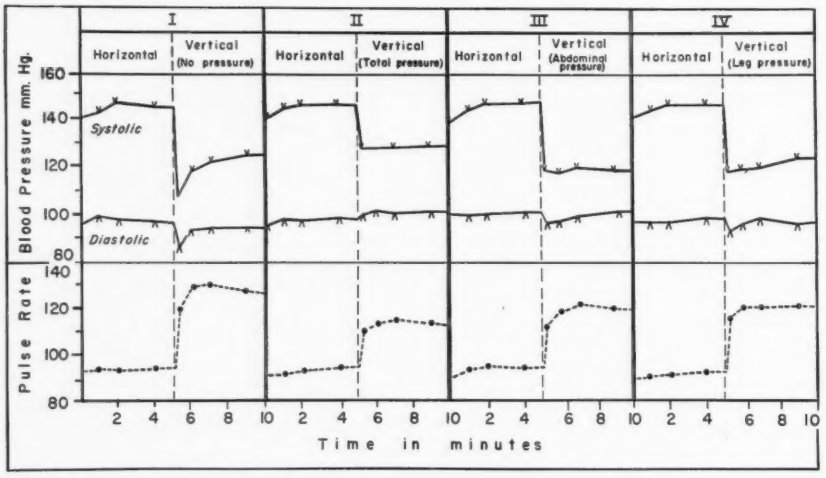

FIG. 2. Circulatory response to change in position from horizontal to vertical following 2 mg. atropine sulfate intramuscularly. Mean response of 20 normal adult males.

showed a considerable and sustained rise with tilting to the vertical, but there was no significant alteration in the systolic pressure (fig. 1). Tilting after external compression of the abdomen or lower extremities resulted in essentially the same response of the systolic and diastolic pressure, although there was a slightly higher diastolic rise during the periods when abdominal compression was applied.

Atropinization caused a marked drop in systolic pressure in all sections with tilting to the vertical position (fig. 2). The greatest initial pressure drop occurred with no compression, whereas, total compression (combined abdominal and lower extremities) resulted in the smallest initial systolic pressure drop. With either abdominal compression, alone, or lower extremity compression, alone, the systolic pressure drop was between these two extremes. The diastolic pressure dropped, with shift to

TABLE 1.—*Effect of Body Pressure on Decrease in Blood Pressure and Acceleration of Pulse Rate at Time of Tilting of 20 Normal Adult Males from Horizontal to Vertical Position Following the Intramuscular Injection of 2 mg. Atropine Sulfate*

Pressure Applied		Effect on Blood Pressure* (*mm. Hg*)		Effect on Pulse Rate† (*per min.*)
		Systolic	Diastolic	
No Pressure	Mean	↓40	↓13	↑37
	Range	(↓4–↓100)	(↑20–↓72)	(↑73–↑20)
	St. Dev.	±27.0	±24.8	±15.8
Leg Pressure	Mean	↓30	↓7	↑31
	Range	(↑10–↓86)	(↑24–↓58)	(↑64–↑12)
	St. Dev.	±25.0	±21.4	±15.3
Abdominal Pressure	Mean	↓28	↓6	↑29
	Range	(0–↓92)	(↑22–↓52)	(↑60–↑6)
	St. Dev.	±24.2	±18.9	±12.0
Total Pressure	Mean	↓18	↑1	↑22
	Range	(↑4–↓50)	(↑24–↓32)	(↑40–↑6)
	St. Dev.	±17.8	±4.6	±9.3

↓ = fall at time of tilting.

↑ = rise at time of tilting.

* Difference between mean values recorded during first minute after tilting and the preceding horizontal position.

† Difference between greatest mean change occurring during five minute vertical test period and the preceding horizontal position.

TABLE 2.—*Comparison of the Effects of 2 mg. Atropine Sulfate and Placebo on Blood Pressure and Pulse of 31 Normal Adult Males Resting Supine for 40 Minutes Following Intramuscular Injection*

Determination		Atropine*	Placebo*	Difference A-P
Systolic Blood Pressure (mm. Hg)	Mean	132	121	11
	Range	96–170	100–146	
	St. Dev.	±15.3	±11.3	
	Probability	less than .01		
Diastolic Blood Pressure (mm. Hg)	Mean	88	72	16
	Range	60–116	55–92	
	St. Dev.	±12.8	±8.1	
	Probability	less than .01		
Pulse Rate (per minute)	Mean	89	68	21
	Range	66–122	54–86	
	St. Dev.	±12.7	±8.1	
	Probability	less than .01		

* Each value represents mean of 124 recordings, each subject having been tested four times.

the vertical position, in all instances except with total compression. These results are recorded in table 1.

The resting horizontal blood pressure was significantly higher during the atropine phase than during the placebo phase. Table 2 lists the mean values following placebo and atropine injections. Five individuals showed a marked increase in blood pressure following the 2 mg. of atropine sulfate. Their average systolic increase was 29 mm. Hg and the diastolic increase was 23 mm. Hg.

Pulse Rate. The mean changes in pulse rate following placebo and atropine are recorded in figures 1 and 2. The radial pulse showed a significant rise when the subjects were tilted to the vertical position whether they had had atropine or placebo. However, there was a sinus tachycardia with atropine and the elevation with tilting was approximately twice as great as it was with the placebo. The greatest rise occurred with no compression and the least rise with total compression following either atropine or placebo. Abdominal and lower extremity compression, alone, resulted in a rise intermediary between the other two vertical records. The differences for atropine are shown in table 1.

The mean resting pulse taken 40 minutes after atropinization was significantly higher than the placebo rate (table 2). The average pulse change for the five subjects who had the greatest rise in arterial blood pressure 40

minutes after atropine injection was only 5 beats per minute higher than the average pulse increase for the whole group.

Syncope. One atropinized subject went into syncope during the first minute in the vertical position without any external compression. He was immediately lowered to the horizontal position and quickly recovered. There was no previous history of syncope, and he showed a normal response after the placebo injection. Syncope did not result when he was tested with abdominal compression or lower extremity compression, alone. This subject was included in the mean with the other 19 subjects in figures 1 and 2 because he represents an extreme rather than an abnormal reaction to the atropine. His data help to emphasize the effect of external body compression at the various sites. Since only the first value of his vertical no-compression period was obtained, the other mean values recorded during the vertical part of section I of figure 1 represent only 19 subjects and give a slightly higher upsweep to the curve since they did not react as acutely to the atropine.

Subjective Effects. The subjects were asked to relate any subjective symptoms or reactions following the injections. All subjects complained of a dry mouth, the time of onset averaging 20 minutes after the atropine injection. There were a few complaints of dull headache, hot flushing of the face, lassitude and mild giddiness or light-headedness. Midriasis was minimal and appeared only near the end of the test period. Palpitation was not complained of by any of the subjects. There were no apparent emotional reactions by any of the subjects to the injections.

Discussion

These studies have demonstrated that 2 mg. of atropine sulfate given intramuscularly will cause relative postural hypotension in healthy young men within 40 minutes. By the use of external compression applied to the legs and abdomen of atropinized subjects, it has been shown that this results from vascular pooling in the legs and the splanchnic area. Changes in arterial blood pressure and pulse rate support this hypothesis.

A comparison of the effects of compression applied to the abdomen or legs separately indicates that the splanchnic area and legs are about equally important reservoirs for the vascular pooling associated with atropinization. This is true when the average results are considered. However, individual cases may show more pooling in one area or the other depending upon undetermined factors. Support of the vascular system by combined abdominal and leg compression is considerably more effective than either leg compression or abdominal compression, alone.

These tests have not elucidated the mechanism by which atropine causes vascular pooling with resultant postural hypotension. However, the results suggest certain sites of action for this drug.

The reaction of these subjects to atropine indicates that there is a partial vagal block (muscarinic) which results in an increase in the resting heart rate. This action of atropine has been well documented.[3-5]

There is also a significant increase in systolic and diastolic blood pressure. The explanation for this may be the increased pulse which can cause a rise in arterial pressure. This is supported by the fact that the rise in mean systolic pressure is not as great as the rise in mean diastolic pressure. Best and Taylor[6] state that pulse rate increases can cause this type of elevation in blood pressure.

However, consideration of individual cases reveals that some subjects had marked elevation in arterial blood pressure with only minimal increases in pulse rate. The five subjects with the greatest blood pressure rise had a systolic pressure increase two and one-half times greater than the entire group and a diastolic increase one and one-half times as much as the average of the other subjects. The same subjects had a pulse increase of only one and two-tenths times the average of the entire group. This indicates that some factor other than tachycardia was acting in some subjects to raise the arterial pressure. This factor may be the action of atropine on the central nervous system. No direct evidence for such a phenomenon was obtained by this investigation. But there are reports of similar

effects on the blood pressure which are attributed to the central excitation by atropine in doses approximating those used here. Bromey,[7] Nalefski,[8] Myer,[9] and Salter[3] have reported increased blood pressure and mental disturbances as criteria indicating central nervous system stimulation. The recent work of Himwich[10] has clearly shown a comparable effect between central nervous system stimulants and large doses of atropine sulfate in rabbits.

The passive change from supine to standing normally initiates reflex changes in the vascular system which are significantly altered by 2 mg. of atropine. Examination of these alterations further helps to explain the action of this drug.

Approximately 40 minutes after the intramuscular injection of 2 mg. of atropine sulfate, the vascular reflex mechanism is not efficient when the subject is tilted to the standing position. There is an immediate sharp drop in systolic pressure which remains uncompensated for about a minute and then slowly rises to the level of the preatropine pressure. The diastolic pressure drops immediately, but not as much as the systolic pressure. It slowly returns to about the pretilt level of pressure. Compared with the placebo phase, the pulse increases more than twice as much when the atropinized subject is tilted, and it remains faster during the standing period.

Since cardiac acceleration is not impaired when the subject is tilted, the default in reflex action is probably located along the vasopressor pathway. This is substantiated by the fact that in the preatropine subject the diastolic pressure is increased in the standing position, whereas, after atropinization, the diastolic pressure drops immediately after standing and slowly returns to the pretilt level. The best proof of decreased vasopressor tone is vascular pooling, which is partially prevented by external compression of the dependent areas.

Three sites of action may be hypothesized for this atropine effect on the vasomotor reflex: ganglionic, peripheral, or central. Marrazzi[11] has shown that large doses of atropine can effectively block transmission by autonomic ganglia and, further, has identified cholinergic and adrenergic mechanisms in the central nervous system.[16] The work of Hamet[12] suggests that atropine may act directly on the vascular smooth muscle. King[13] believes that atropine has central nervous system stimulatory effects, either by direct stimulation of the medullary autonomic centers or by an atropine depression of the higher centers.

Ganglionic blockage would explain postural hypotension during passive standing. However, if ganglionic block, alone, was acting, there should be a relative hypotension even when the subjects were in the supine position. Finnerty[14] showed that hexamethonium causes hypotension in supine subjects. Goetz[15] reported that pentamethonium did not cause any change in arterial blood pressure when given to subjects in the supine position, but that the subjects did develop hypotension with an increase in pulse rate when standing. Contrary to the action of accepted ganglionic blocking agents, atropine causes a significant relative hypertension in the supine position in the majority of subjects.

Any attempt to explain the action of atropine by a direct effect on the vascular smooth muscle encounters the same difficulty. With direct acting drugs such as amyl nitrite, hypotension has been observed to occur in the supine and standing positions. If atropine had a similar action, there should not be the definite hypertensive trend when the patient is supine.

This action of atropine also cannot be explained on the basis of central stimulation or depression, alone. However, from the preceding discussion, a hypothesis may be suggested that the action of atropine on vasomotor tone is twofold, namely, central excitation and ganglionic blockade. With this hypothesis the supine hypertension may be explained as the result of increased activity in the vasopressor center which causes a relative hypertension in spite of a partial ganglionic block. During passive standing the partial ganglionic block is sufficient to prevent effective vasoconstriction. The result is pooling of blood in the dependent areas of the body.

The use of graded doses of atropine, in larger doses than those employed here, might supply

a more definite answer regarding the exact mechanism of this vascular pooling.

In a recent survey, Gordon and Frye[17] have found that atropine toxicity is rare, but that when it occurs it is frequently due to an atropine sensitivity rather than excessive dosage. The occurrence of syncope in some otherwise normal subjects, although most subjects react only with mild orthostatic hypotension, suggests that measurement of orthostatic hypotension following atropine administration may serve as a test of sensitivity to this drug.

Summary

1. It has been determined that the main effect of 2 mg. of atropine sulfate intramuscularly on the cardiovascular system is a decreased vascular tone with pooling in the dependent areas of the body when standing. Pooling occurs in both the splanchnic and peripheral vascular beds.

2. Application of external compression to the abdomen and lower extremities allowed easier cardiovascular compensation for the postural changes. Compression of the legs and abdomen was much more effective than compression of either area, alone.

3. The effects of 2 mg. of atropine demonstrated in this investigation are partial vagal block, partial ganglionic block and central excitation. In the supine position, central excitation and vagal block overbalance ganglionic blockade with a resultant relative hypertension. In the standing position, the ganglionic block is sufficient to prevent adequate vasoconstriction, and there is relative postural hypotension.

Sumario Español

1. Se ha determinado que el efecto mayor de 2 mg. de sulfato de atropina intramuscular en el sistema cardiovascular es un decremento en el tono vascular con resultante estancamiento en las partes dependientes cuando el sujeto permanece erecto. El estancamiento ocurre tanto en el cama vascular esplácnica como en la periferal.

2. La aplicación de compresión externa al abdomen y las extremidades inferiores permitió una compensación cardiovascular más fácil para los cambios posturales. La compresión de las piernas y el abdomen fué mucho mas efectiva que la compresión de una de estas areas a la vez.

3. Los efectos de 2 mg. de atropina demostraron en esta investigación ser, bloqueo vagal parcial, bloqueo gangliónico parcial y excitación central. En la posición reclinada, la excitación central y el bloqueo vagal sobrebalancearon el bloqueo gangliónico con una hipertensión relativa resultante. En la posición erecta, el bloqueo gangliónico es suficiente para evitar vasoconstricción adecuada, y resulta en una hipotensión postural relativa.

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The Correction of Electrolyte Deficits in Cardiovascular-Renal Disease

By F. R. SCHEMM, M.D., AND A. A. CÁMARA, M.D.

DR. SCHEMM: We are all familiar with the syndrome of sodium depletion and the resultant fall in extracellular fluid volume that occurs among the so-called salt-losing hypertensives and nephritics. Such patients, because of poor kidney function, lose sodium through the urine in excess of their intake of this electrolyte. The symptomatology produced is very much like that seen in Addison's disease: weakness, fall in blood pressure, anorexia, nausea, vomiting and cramps. Today we shall concern ourselves with the more difficult situations arising in patients with the added problem of edema.

A PHYSICIAN: Dr. Schemm, before you go any further, will you please explain the mechanism by which some nephritics and hypertensives become salt-losers? You mentioned that such patients have "poor kidney function," but this phrase is also used to explain the formation of edema.

DR. SCHEMM: I knew that using the ambiguous phrase, "poor kidney function," would lead to this question, and I am glad you asked it.

As you know, in health the *volume* of the extracellular fluid as well as the *concentration* of the electrolytes (mainly sodium) dissolved in this fluid are, within narrow limits, maintained constant. This means then that the healthy individual maintains sodium and water balance (i.e., intake equals output) from day to day. We do not need to go into the details at this point, but suffice it to say that the ultimate task of balancing intake against output falls on the kidney tubules. Even on as low a sodium intake as 150 to 200 mg. daily (6.5 to 8.7 mEq.) the normal kidneys are able to maintain balance by a sharp reduction in the urinary output of sodium, i.e., there is *virtually complete* reabsorption of all the sodium present in the glomerular filtrate. This means that *osmotic work* is done by the kidney tubules. Now, the badly damaged kidneys of patients with advanced nephritis or terminal hypertension are unable to perform the necessary amount of osmotic work; hence much of the filtered sodium remains unabsorbed as the glomerular filtrate courses through the distal tubules, and the unabsorbed sodium appears in the urine, irretrievably lost to the organism. It is little wonder then that such patients easily get into trouble even with moderate restriction of dietary sodium; for, like otherwise untreated Addisonians, they require supplementary doses of sodium salts to maintain sodium balance. I should like Dr. Cámara to comment on the concept of edema formation.

DR. CÁMARA: I certainly object to the use of the phrase, "poor kidney function," to explain the mechanism of edema formation. The main disturbance in the formation of edema, be it the edema of congestive heart failure, of glomerulonephritis, or of cirrhosis of the liver, is an excessive tubular reabsorption of sodium from the glomerular filtrate, resulting in an abnormal retention or *positive* balance of sodium, with a secondary retention of water in proportionate amounts such that the concen-

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tration of sodium in the edema fluid is usually the same as its concentration in normal interstitial fluid. In other words, the kidney tubules in edema are doing *more* osmotic work with regard to sodium than they should. It is, then, only in the sense that excessive tubular osmotic work is being done that kidney function in edema may be regarded as "poor."

More recently experimental data have been obtained purporting to show that in some cases of edema, excessive retention of water might be the primary change, followed by increased reabsorption of sodium. We shall elaborate more on these points as we discuss the problems encountered in some of the patients to be presented today.

A PHYSICIAN: Most of the cases of "salt losers" reported in the literature are sodium losers. Are there also "potassium losers" in the same sense?

DR. SCHEMM: Yes, there are potassium losers, and one should be on the lookout for them especially in two situations; (1) cardiacs and nephritics, with edema previously responsive to treatment, who become refractory to treatment, and (2) patients with far-advanced kidney disease, some of whom become spontaneous potassium losers.

We have several patients in our series who belong to the first category. In the early course of their trouble, they get rid of their edema on the diuretic regime without developing potassium deficiency. As in normal subjects, their kidney tubules are able to reabsorb selectively the necessary amount of potassium from the glomerular filtrate to maintain potassium balance, even in the face of a diuresis of sodium caused by mercurial administration. Later on, for some unknown reason, the kidney tubules lose the power of selective reabsorption of potassium and a dose of mercurial diuretic causes as much, if not more, urinary output of potassium than of sodium. At this stage the edema becomes resistant, but we have seen such patients respond to treatment again with administration of potassium salts by vein or by mouth.

Let me briefly review with you the case of a 50 year old patient, R. M., to illustrate the situation I have just described.

This woman had severe rheumatic heart disease with a marked degree of mitral and aortic valve involvement. She had suffered from rheumatic fever when she was 18, and had been aware of persistent irregularity of heart action since the age of 32. When first seen in 1949 at age 53, she had been in severe congestive failure for at least two years. The edema readily cleared on the usual diuretic regime. From then on there followed a long series of admissions with a progressively intractable edema. Sodium and potassium balance studies were carried out on each of her many admissions to the Metabolic Unit. It was during the course of a hospitalization in 1950 that marked urinary losses of potassium with mercurial administrations were first discovered. On one occasion, for example, an intramuscular injection of 3 ml. of Thiomerin resulted in a urinary output of 216 mEq. of potassium as compared to 118 mEq. of sodium on the same day. This meant negative balance of potassium especially on certain days when food intake was poor, and was reflected in a drop of plasma potassium to definitely hypokalemic levels (1.9 to 2.1 mEq. per liter). Her edema started to clear up after attention was paid to maintenance of potassium balance which required an intake of 6 Gm. of potassium chloride daily.

Potassium chloride may be given intravenously (2 to 4 Gm. in 1000 ml. of 5 per cent dextrose, depending on the patient's needs) or by mouth. The latter route is preferred whenever the patient can tolerate it. We give it in a capsule, buffered with an equal amount of calcium carbonate. Some patients will complain of burning despite the calcium carbonate; in this event they are given potassium bicarbonate instead. Each gram of potassium chloride supplies 13.4 mEq. of potassium, whereas a gram of potassium bicarbonate yields only 10 mEq. of this electrolyte.

DR. CÁMARA: While working with Dr. Newburgh in Michigan I had the opportunity to study potassium metabolism in a number of advanced cases of renal damage in whom the volume of the glomerular filtrate had been reduced to as low as 4 to 10 liters per 24 hours. Interestingly enough, we found in these patients either normal or low plasma potassium levels, in contrast to the usual reports of potassium intoxication in severe renal disease The existence of potassium deficiency in these patients was demonstrated not only by the finding of hypokalemia but also by the avidity with which administered potassium was conserved, as shown by potassium balance studies.

A typical case in our series was D. M., a 49 year old man who entered the hospital in stupor following several convulsive seizures. There was severe uremia and anemia. The glomerular filtrate volume as measured by the endogenous creatinine clearance was only 6.6 liters in 24 hours. Retrograde pyelograms disclosed polycystic kidneys. Little improvement was seen following blood transfusions and infusions of dextrose, saline and sodium lactate solutions, but after addition of potassium chloride to the intravenous fluids there was rapid improvement in sensorium and eventual recovery. Unfortunately, the plasma potassium level was not determined prior to administration of potassium chloride, but even after he had received 16 Gm. of it in 36 hours, the serum potassium concentration was only 3.2 mEq. per liter. Thereafter, he received orally 12 Gm. of potassium bicarbonate daily until normal serum potassium levels were attained. This man was able to go back to work as a machinist for one year before he succumbed to total kidney failure.

A PHYSICIAN: Dr. Cámara, would you classify this patient in the second category of potassium losers that Dr. Schemm previously mentioned?

DR. CÁMARA: Definitely. Note that this patient was not on a diuretic regime but had spontaneously developed potassium deficiency. I forgot to mention that he had had anorexia for two weeks prior to admission, making for a poor food intake during that period. Potassium deficiency should have been suspected from the beginning owing to that fact alone.

In patients with advanced kidney disease we have demonstrated that renal tubular *secretion* of potassium takes place as a compensatory mechanism which prevents potassium intoxication (in normal subjects, about 90 per cent of the potassium in the glomerular filtrate is *reabsorbed*). This mechanism obviously plays a major role in the development of potassium deficiency when the food intake is poor. Other factors which contribute to a continuing large urinary loss of potassium in kidney disease are impairment of the capacity for ammonia production and reduction in the ability to produce an acid urine, thus necessitating increased excretion of fixed base whenever large quantities of acid ions are presented to the kidneys for excretion (such as follows the administration of ammonium chloride or ingestion of a high protein diet). Usually the loss of fixed base in such a situation consists primarily of sodium. However, we have demonstrated that when dietary sodium is sharply restricted, an internal stimulus for the kidneys to conserve sodium develops, and the fixed base excreted during ammonium chloride administration may then consist almost entirely of potassium.

Dr. Schemm, I am afraid all this talk on potassium has been a digression from what you had originally intended to discuss.

DR. SCHEMM: Not at all, Dr. Cámara. These remarks on potassium are by no means a digression; it just shows that sodium and potassium cannot be divorced from each other in any discussion of electrolyte metabolism.

The problem of electrolyte deficits in patients with cardiovascular-renal disease is truly a fascinating and complex one. It is a problem of many facets which anybody interested in this field is bound to encounter. Take, for example, the problem of severe hyponatremia developing in cardiac patients with *resistant* edema as a result of the use of mercurial diuretics. Here, one is faced with a dilemma: hyponatremia cries out for sodium replacement, while edema interdicts its administration. The problem is, to paraphrase Shakespeare, to give or not to give sodium salts. When the degree of hyponatremia is severe enough to produce symptoms such as mental confusion or even coma, "cogwheel" resistance to passive movement of the extremities, and other symptoms, one is forced to risk worsening of edema and administer sodium salts.

A 65 year old woman, B. S., whom we had in the Metabolic Unit a year ago exemplifies such a problem. She had rheumatic valvular heart disease with mitral stenosis, and possibly a concomitant hypertensive and arteriosclerotic heart disease. She had been in frank congestive failure for two years prior to admission. When she came to the Unit she was orthopneic and had frequent severe episodes of paroxysmal dyspnea. The heart was markedly enlarged and was fibrillating. She had bilateral hydrothorax, hepatic passive congestion, ascites, and deep dependent edema.

Electrolyte balance studies were carried out in this patient as is usually done with edematous patients admitted to the Metabolic Unit. The plasma sodium concentration on admission was 143 mEq. per liter. She received 1 ml. of Thiomerin on the third, and again on the sixth hospital day, with so-

dium diuresis but with practically no weight loss. On the twelfth day, she weighed 2.6 Kg. more than she did on the day of admission, despite the fact that she had had the mercurial diuretic twice and a total of 1,350 ml. of chest fluid had been aspirated from both pleural cavities. On that day the patient was in a coma. The plasma sodium was found to have dropped to 118 mEq. per liter, while plasma potassium was at a normal value of 4.4 mEq. per liter.

At this point we felt we were licked unless something drastic were done. The degree of hyponatremia evidently was great enough to account for the coma. We also knew that no further progress with regard to clearing of edema could be made, knowing from previous experience that hyponatremia in itself has an antidiuretic effect.

A PHYSICIAN: I would like to know if you have found among your patients a particular critical level of plasma sodium at which symptoms begin to appear.

DR. SCHEMM: No, there is no such critical level that applies to all the patients. I have seen a patient who was only mildly disoriented at a plasma sodium level of 103 mEq. per liter, and, on the other hand, I have witnessed hallucinations and confusion set in with a plasma sodium concentration reduced only to 124 mEq. per liter. I would imagine that several factors such as the rate of drop of concentration of plasma sodium and the state of body stores of other minerals (potassium, calcium, magnesium, and others) determine the critical low level of plasma sodium at which symptoms appear.

To go back to our patient B. S., she promptly roused from her coma within a few hours after administration of 24 Gm. of sodium chloride (800 ml. of 3 per cent sodium chloride solution) with 200 ml. of molar sodium lactate solution. This infusion gave her a total of 610 mEq. of sodium. By the following day the plasma sodium concentration had risen to 148 mEq. per liter. Following this correction she responded to three doses of Thiomerin with an edema weight loss of 9 Kg. in the next 11 days during which she received more sodium chloride and sodium lactate solutions both in hypo- and hypertonic forms. The plasma sodium at the end of this particular period was 145 mEq. per liter.

A PHYSICIAN: This all sounds paradoxical to me. In the management of edema we aim at the excretion of excess body sodium which is responsible for the excessive volume of the interstitial fluid, yet in this case, you achieved results by further use of a mercurial diuretic, truly enough, but also by simultaneous administration of sodium salts.

DR. SCHEMM: There are many aspects of edema that we do not fully understand, to be sure. In the case of patient B. S., our balance studies showed that during the 10-day period when the plasma sodium dropped from 143 to 118 mEq. per liter there was a negative sodium balance of 306 mEq. associated with a weight gain of 2.6 Kg. instead of a weight loss. During the succeeding 11 days when sodium replacement was carried out, she exhibited a negative sodium balance of 341 mEq. with a weight loss of 9 Kg. and correction of hyponatremia. I should mention at this juncture that we gave her a course of corticotropin therapy during the second period under consideration, which may well account for the altered favorable response to the mercurial diuretic. We shall discuss corticotropin later in connection with other patients.

DR. CÁMARA: The annoying failure of this patient to lose edema despite *negative* sodium balance during the first period is typical of the behavior of certain badly degenerated or what appeared to be terminal cases that we have seen.

I think this is a good place to elaborate further on the current concepts of edema formation. Dr. Schemm pointed out in the beginning of this conference that the extracellular fluid in health is characterized by constancy of concentration of each of its inorganic constituents, and also by relative fixity of its volume. These two features are under separate control, working through the kidneys which are the final guardians of the "milieu interne." The reabsorption of sodium is controlled by the adrenal cortical hormone, but the body content of water is governed by the antidiuretic hormone through regulated reabsorption of water. Constancy of concentration of sodium is maintained in health, so that there must be *coordinated* activity of these functions, causing the rate of reabsorption of sodium to keep pace with the reabsorption of water. At the present stage of our knowledge, we do not know the

ultimate nature nor the seat of this *coordinating mechanism*.

In edema, whether it be the anasarca of heart failure, the nephrotic edema of glomerulonephritis, or the ascites of cirrhosis of the liver, the organism has become abnormally geared to maintain an excessively large volume of extracellular fluid. However, except in the far-advanced or deteriorated cases, coordination between the two factors which govern renal tubular reabsorption of sodium and of water is still maintained, as evidenced by persistence of normal concentration of sodium in the extracellular fluid, including edema fluid. In the *far-advanced* cases, be they cardiacs, cirrhotics, or nephritics, the stimulus for maintenance of an abnormally large volume of extracellular fluid is so intense that when measures such as dietary sodium restriction and mercurial diuretics are instituted for the prevention of further accumulation and for the elimination of excess body sodium, normal sodium concentration in the extracellular fluid is sacrificed for volume; i.e., such patients do lose body sodium, but retain disproportionately excessive amounts of water, resulting in the picture of edema with hyponatremia.

DR. SCHEMM: As previously pointed out, hyponatremia in itself has an antidiuretic effect, and so an impasse is reached.

We have tried the trick of simultaneously administering sodium chloride solutions and a mercurial diuretic in the situation just described.

The case of H. M. on one of her admissions to the Unit presented a similar problem in which edema had developed in the face of abnormal electrolyte loss through diarrhea. She was 38 years old, had rheumatic heart disease with a severe grade of mitral stenosis and moderate mitral insufficiency, and had undergone a mitral valvuloplasty a year previously. Even after surgery she had to be kept on a diuretic regimen to keep her free of recurrent edema. Nine days prior to this particular admission she contracted gastroenteritis with frequent loose bowel movements which persisted until admission. Four days after onset she developed an acute upper respiratory tract infection and from then on she became progressively worse, manifesting dyspnea, cyanosis, cough, and culminating in several emeses just before admission. She noted a rather rapid development of edema with a total weight gain of 9 pounds during this episode. On admission she exhibited orthopnea, deep cyanosis, auricular fibrillation with a rapid ventricular rate, marked pulmonary passive congestion, a tender liver that extended 3 inches below the right costal margin, some ascites, and leg edema. There was no improvement during the first hospital day despite a booster dose of digitalis and oxygen and she was even worse the following morning. On this day, plasma sodium and potassium were reported to be 135 and 4.3 mEq. per liter, respectively. She was then given 2 ml. of Thiomerin intramuscularly and later in the day she received 500 ml. of 2 per cent sodium chloride and 1000 ml. of isotonic sodium chloride, making a total of 320 mEq. of sodium. There was a dramatic clinical improvement within a few hours following the two infusions. The following day the weight was unchanged; but with correction of plasma sodium to 143 mEq. per liter, she responded to two subsequent doses of Thiomerin with loss of 10 pounds of edema weight in eight days and maintenance of normal plasma sodium values.

We have administered sodium chloride to edematous cardiac patients in still another situation. These are the patients who become mercurial fast after having lost only about half of their edema. These patients respond again to mercurials and lose the rest of their edema, but only after a "rest period" during which it is best to relax dietary sodium restriction or even give sodium chloride intravenously. During the resistant phase, in spite of the excess volume of interstitial fluid still present, such patients exhibit a sharp drop in venous pressure, oliguria and those clinical evidences of hypovolemia of the blood, so well described by Lyons and Pitts in nonedematous normals who have been given mercurial diuretics. In these cases, we suspect that a too rapid fall in tissue pressure with initial loss of edema had disturbed hemodynamics and caused the development of a seemingly intractable edema.

A PHYSICIAN: I am able to follow your line of reasoning in administering sodium salts to edematous subjects under the circumstances you have just described; however, I am completely in the dark as to the rationale behind the use of corticotropin in patient B. S. who, if I remember correctly, was in congestive heart failure. My instruction in physiology and endocrinology would lead me to believe that corticotropin would only enhance sodium re-

tention and that it would be contraindicated in congestive heart failure.

DR. SCHEMM: Unfortunately, or rather fortunately, our experience with corticotropin in congestive failure has belied its known effects on the renal excretion of sodium in normals. You may well realize the fear and trepidation with which we used this hormone for the first time on a case of congestive failure in the spring of 1952. Since then we have had the opportunity to use it in 17 other cases. We have been highly gratified with the beneficial results obtained in 15 of these cases, more so when one considers the fact that the patients on whom it was used were selected on the basis of intractability of edema to the usual diuretic measures (including mercurial diuretics) and/or myocardial insufficiency of a degree sufficiently severe to warrant a classification of "hopeless cases."

Electrolyte balance studies on these patients show that corticotropin does one of two things; i.e., it causes a *spontaneous* profuse diuresis of sodium starting either on the third to sixth day of its administration (it is given in doses of 15 to 25 U every six hours for 10 to 12 days) or after its discontinuation; and, in those cases where no spontaneous diuresis occurs, it produces an altered response to mercurial diuretics, making the latter effective where they had been completely useless before. Furthermore, apropos our subject today we have seen it in a few instances correct hyponatremia in an edematous subject without necessitating supplements of sodium salts, as was the case with D. K.

This 69 year old man from Canada had had a coronary occlusion eight years previously. He became aware of exertional dyspnea four years, and of dependent edema two and one-half years prior to his admission here. The edema had lately been getting unrelentingly worse despite adherence to a low-sodium diet and the use of oral as well as parenteral mercurial diuretics, the latter having been given as often as three times a week. He was obviously in severe congestive failure when we saw him, having a marked generalized fullness of the body with definite pitting in the dependent parts, moderate ascites, splenomegaly, and a tender liver that was ballotable for 4 inches below the right costal margin. On the third hospital day, a trial dose of 2 ml. of Thiomerin given intravenously was "rewarded" by a urine output of 500 ml. which contained 0.7 mEq. of sodium, and further weight gain of 3.5 pounds. On the fifth day, when corticotropin was started he was much worse, having more edema, persistent oliguria (despite adequate water intake), annoying constant hiccups, anorexia, and a severe degree of hyponatremia (116 mEq. per liter). During the initial four days on corticotropin (25 U every six hours) there was a weight gain of 9 pounds, but starting on the fifth day there occurred a continuing diuresis from day to day culminating in a total edema weight loss of 40 pounds in 13 days.

A PHYSICIAN: To say that your results in this patient were spectacular is an understatement, but how did corticotropin accomplish that feat?

DR. SCHEMM: When we started using corticotropin in "hopeless" cases of congestive failure, it was our thesis that benefit might be obtained from its action on some organ-system of the body other than that concerned with sodium retention. This could possibly be in the form of improvement of the myocardium. Forgive me for talking in such vague terms for I would rather have the physiologists and endocrinologists come forth with an explanation, while we confine ourselves to the reporting of factual observations.

Be that as it may, what I really wanted to point out in this case was the fact that the diuresis induced by corticotropin was mainly a *water* diuresis, the total urinary sodium output from the fifth to the ninth day of its administration being only 4.3 mEq. The drop in body weight during this five-day period under consideration was 17 pounds. The plasma sodium concentration during the same period rose from 122 to 133 mEq. per liter, and finally to 142 mEq. per liter when he was discharged nine days later after having lost 40 pounds of edema weight. I want to emphasize the fact that this correction was accomplished without giving supplements of sodium salts. His eagerness to get back to his family in Canada made us relent and we gave him two doses of Thiomerin to hasten the clearing of the remaining vestige of edema during the last few days of his sojourn.

A PHYSICIAN: I am fascinated by this approach to the problem of resistant edema. No doubt you are all aware that there is an increasing number of reports in the literature of cases of edematous cardiacs or nephritics who

become refractory after a while on a program which includes strict dietary sodium restriction, acidifying drugs like ammonium chloride, and intermittent doses of the mercurial diuretics. It would appear that for some of these patients at least, a new vista, a new avenue of hope has been opened by this paradoxical effect of corticotropin.

DR. CÁMARA: Lest our statements lead to the promiscuous and injudicious use of corticotropin in the situation just described, especially in heart disease, I would like to make a few comments on the regimen which we ordinarily use in the management of edema and which is maintained during and after corticotropin therapy. Of course we make certain before starting that the adrenal cortices of the prospective patient will respond to the hormone; for evaluation of this, we rely rather heavily on the Thorn test. Our patients receive a neutral or acid-residue diet which contains from 9 to 30 mEq. of sodium daily, depending on the patient's caloric intake. The emphasis is on the acid reaction of the diet residue rather than on strict sodium restriction, up to a certain point of dietary sodium intake. Ammonium chloride is administered daily in doses of 1.5 to 4 Gm.; it is given in loose powder form buffered with equal amounts of calcium carbonate in a capsule. The few patients who do not tolerate this are given the enseal form of ammonium chloride. Strict attention is paid to fluid intake which is kept between 2500 to 4000 ml. daily in the majority of cases. Daily fasting weights are obtained every morning. Our facilities at the Metabolic Unit enable us to determine daily 24-hour excretions of sodium, potassium and chloride in the urine. Those patients who do not diurese spontaneously by the fifth or sixth day and who manifest an alarming rate of weight gain are given intermittent doses of Thiomerin. A close clinical watch of of the lungs in particular is kept. Adjuvant measures such as digitalis, oxygen, sedation and rest are not neglected.

I should also mention that at the outset the prospective candidate for corticotropin therapy is carefully evaluated for the presence of conditions which constitute known contraindications to the use of corticotropin, other than congestive failure.

A PHYSICIAN: If such contraindications are present, then what?

DR. CÁMARA: Then we are faced with a dilemma indeed, and we find our way out by carefully balancing the risks against the anticipated beneficial effects from its use. If all other measures have been tried to no avail and the patient continues to sink, then we try to pull him up by his bootstraps by using corticotropin, regardless of the contraindications. This does not mean that caution is thrown to the winds. I might briefly relate the case of F. R. to illustrate my point.

He was a 54 year old man with hypertensive heart disease who came to us within a few hours following a sudden transient episode of pulmonary edema. Following admission serious complications developed rapidly despite institution of the usual measures. Within the span of a few days he developed a pleuropericarditis (with fever and leukocytosis) followed immediately by confusion and marked agitation (possibly resulting from barbiturates and opiates used for sedation), auricular fibrillation, and then an acute dilatation of the left ventricle (as shown by serial chest roentgenograms) with the clinical picture of paroxysmal dyspnea, Cheyne-Stokes respirations of a marked degree, progressively and rapidly worsening pulmonary passive congestion, culminating in right sided failure with hepatic passive congestion and peripheral edema.

At this point we remembered our good friend corticotropin, but the following considerations made us pause for a while: (1) he had just had a recent episode of pulmonary edema, (2) he was known to have a duodenal ulcer with a flare-up only two weeks previously, (3) there was infection present (pleuropericarditis) which was being treated with antibiotics, and (4) confusion and agitation had set in. I am sure all of you will agree that each one of the above situations constituted a serious contraindication. After much deliberation, we decided to proceed with corticotropin anyway, but with the following precautions: (1) prophylactic doses of Probanthine were given regularly, (2) all stools were examined for occult blood and daily determinations of red blood cells and hemoglobin were done (blood was held in readiness all the time), (3) adequate doses of antibiotics (penicillin, streptomycin, and erythromycin) were maintained, (4) daily fluid intake of 3000 to 4000 ml. was assured by infusions of 5 per cent dextrose in distilled water, (5) mild acidification with small doses (2 Gm. daily) of ammonium chloride with the intravenous infusions was insti-

tuted and (6) we prayed as fervently as we knew how.

A profuse, spontaneous and continuing diuresis started on the third day of corticotropin administration with eventual clearing of all signs of peripheral edema and of pulmonary and hepatic passive congestion. The edema weight loss totalled 15 pounds in 10 days. To make a long story short, this patient's response to corticotropin has been the most spectacular yet that we have had in our series. A chest roentgenogram taken a week following corticotropin therapy showed that the myocardium had regained its tone, the size of the heart having returned to that prior to the onset of acute dilatation. The mild but significant degree of hyponatremia (132 mEq. per liter) was corrected (to 147 mEq. per liter), as in patient D. K., without the use of sodium salt supplements.

DR. SCHEMM: So much now for corticotropin. We could talk for another hour about our exciting experiences with this hormone and turn the conference into a symposium on corticotropin, but, there is another facet of the problem of electrolyte deficits in cardiovascular-renal disease that I would like to touch on before we adjourn. This concerns water and electrolyte replacement in patients who develop serious gastrointestinal and surgical complications. Recognition of the need for plain water replacement besides the correction of electrolyte deficits in these patients is of paramount importance. Some of the common pitfalls include an underestimation of the water lost by vaporization through skin and lungs especially in the presence of fever and during hot weather, failure to recognize the fact that loss of gastrointestinal secretions (through vomiting, gastric suction, and diarrhea) means loss of fluid which is hypotonic with regard to sodium and therefore represents more loss of water in proportion to sodium, and failure to take into account a previously existing dehydration. Preoccupation with the electrolyte deficits often leads to underestimation of plain water needs, and administration of isotonic or hypertonic salt solutions leads to anuria and increasing azotemia. The results can be disastrous if, at this stage, the physician satisfies himself with a diagnosis of "shut down" kidneys or "post-operative nephritis" instead of attempting rehydration with plain water (5 per cent dextrose in distilled water) along with replacement of electrolyte deficits.

The case of a 58 year old housewife, R. S., is a beautiful illustration of this point. She had been hypertensive for 17 years and for 15 years had had exertional dyspnea and intermittent dependent edema. A cerebrovascular episode three years previously had caused a right-sided hemiparesis. During the last six years prior to this particular admission she had had repeated abdominal pain attributed to cholelithiasis. The day before she came in she had a sudden onset of diarrhea with frequent watery stools, generalized abdominal pain, nausea and vomiting. She waited 24 hours before seeking admission to the hospital. By that time she was acutely ill and obviously dehydrated. The blood pressure was down to 80/60 from her usual hypertensive level of 220/110. The rectal temperature was 102.4 F. and the pulse rate 100 per minute. The skin was cold and clammy. There was some cyanosis, but no dyspnea or jaundice. The fundi showed grade II hypertensive retinopathy. The tongue was dry and she complained of thirst. The heart was moderately enlarged and had a gallop rhythm. There were no abnormal lung findings. The abdomen was distended with gas-filled intestinal loops and rumbled with increased peristaltic activity. No abnormal masses could be palpated in the abdomen. Laboratory reports included a normal urine, transient leukocytosis and an electrocardiogram showing digitalis effect. A gall bladder roentgenogram showed multiple gall bladder stones. Gastrointestinal x-ray studies and intravenous urograms were negative. The clinical impression was a severe acute gastroenteritis occurring in a patient with cholelithiasis. Gastric suction was instituted and she was given intravenous fluids, antibiotics and sedatives. She got progressively worse and on the fourth day had major convulsions. The blood urea nitrogen on that day was found to be 100 mg. per 100 cc., while the plasma chloride value was at the unbelievably low level of 47.8 mEq. per liter. It was on that day that she was referred to us and was then transferred to the Metabolic Unit. The water and electrolyte balance data are extremely interesting and I would like to have them projected for you on the screen. (See table 1.)

In table 1 the intravenous fluids have been broken down into isotonic solutions (with regard to sodium and/or ammonium chloride administered) and plain water, meaning 5 per cent dextrose in distilled water. For example, 1000 ml. of 0.9 per cent sodium chloride is listed as 1000 ml. of isotonic solution, whereas 1000 ml. of 0.45 per cent sodium chloride is listed as 500 ml. of isotonic solution plus 500 ml.

TABLE 1.—*Fluid and Electrolyte Data on Patient R. S., 58, F.*

	General Medical Floor			Metabolic Unit						
Hospital Day	1	2	3	4	5	6	7	8	9	10
Fluid intake, ml.										
(1) Oral	0	0	0	220	30	630	900	675	1310	280
(2) I. V.										
(a) Isotonic	1000	1300	1000	4000	3000	2000	3000	1000	500	500
(b) Plain H_2O	0	3000	3000	2000	3000	5000	4000	4500	4500	2500
(3) Total	1000	4300	4000	6220	6030	7630	7900	6175	6310	5480
Body weight, Kg.	—	—	—	62.6	61.6	61.7	61.3	60.9	61.0	60.0
Urine										
(1) Volume, ml.	30	325	375	3800	3110	3100	3870	3500	3530	3830
(2) Sodium, mEq.	—	—	—	27.4	8.4	8.1	11.5	10.5	8.0	11.5
(3) Chloride, mEq.	—	—	—	4.1	3.6	6.4	11.6	11.3	10.6	15.9
Gastric suction										
(1) Volume, ml.	1375	1900	3675	2275	2300	2950	1550	175	0	0
(2) Sodium, mEq.	—	—	—	46.8	190	277	132	6.5	0	0
(3) Chloride, mEq.	—	—	—	56.0	238	290	125	6.0	0	0
Electrolyte replacement in I.V.'s										
(1) Sodium, mEq.	154	200	154	308	308	154	438	154	77	77
(2) Chloride, mEq.	154	200	154	476	392	238	419	154	77	77
Plasma values										
(1) Sodium, mEq./L.	—	—	—	120	—	149	135	144	—	151
(2) Chloride, mEq./L.	—	79.0	67.0	47.8	—	79	79	86	—	98.8
(3) CO_2C.P., mEq./L.	—	28.8	—	34.1	—	29.2	26.8	29.0	—	25.8
(4) Sp. gravity	—	—	—	1.0297	—	—	1.0244	1.0222	—	—
(5) Blood urea N, mg.%	—	57	85	100	—	51	36	14	—	11

of plain water, which really are its equivalent. Most of the electrolyte replacement was carried out in the form of the hypotonic (half-strength) sodium chloride solution which provided adequate amounts of water along with the needed electrolytes, as one can easily see in the Fluid Intake column.

Note during the first three days when she was on the general medical floor that both electrolyte and plain water replacement fell short of her requirements as shown by marked oliguria, rising blood urea nitrogen, high plasma specific gravity, and low plasma sodium and chloride values at the time she was transferred to the Unit. With vigorous water and electrolyte replacement, the oliguria was promptly corrected; the blood urea nitrogen rapidly returned to normal values while the electrolyte pattern was simultaneously being corrected. I want to direct your attention to the Urine column to emphasize the fact that the daily urinary excretions of sodium and chloride were small despite the copious urinary volumes from day to day. It demonstrates the "wisdom" and ability of the kidneys to conserve electrolytes when they are needed by the organism. The fact that no edema was produced by this high fluid regimen is also worth mentioning. There was in fact a weight loss of 2.6 Kg. from the fourth to the tenth day. The patient improved steadily and subsequently underwent a successful cholecystectomy.

A PHYSICIAN: I have long wanted to see data of this sort ever since I became interested in your work, Dr. Schemm. To me they refute the oft-repeated contention that in such a situation as you described, forcing of water will result in "washing out" of the electrolytes; but do not hypotonic solutions such as 0.45 per cent sodium chloride have deleterious effects on the

red cells and the plasma solutes, particularly the proteins?

DR. SCHEMM: I presented the same type of data at the "Salt and Water Festival" sponsored by the National Heart Institute in Atlantic City in April 1949, but I do not recall having seen the proceedings of the symposium published. You asked an interesting question with regard to hypotonic solutions which we ourselves have tried to answer by studies on patients and on ourselves. These studies were designed to see whether hypotonic solutions (0.45 per cent sodium chloride in distilled water and 2.5 per cent dextrose in distilled water) caused hemolysis of red cells and dilution of the plasma constituents. The subjects received within 28 to 70 minutes 1000 ml. volumes of these hypotonic solutions and each time the following determinations were done before, immediately after, and one hour after the infusion: *plasma* hemoglobin, plasma specific gravity, proteins, erythrocyte count, hematocrit, hemoglobin, osmotic pressure, sodium and potassium. The same data were obtained in these subjects using isotonic solutions of sodium chloride and glucose. We found that hypotonic solutions did not cause intravascular hemolysis of red cells as judged by absence of *plasma hemoglobin* after their administration. Values for plasma specific gravity, osmotic pressure, proteins, erythrocyte count, hemoglobin, hematocrit and sodium showed a slight but insignificant dilution immediately after infusion, but they returned to preinfusion values an hour later. The same phenomenon was observed with *isotonic* solutions and curiously enough, such a dilution effect was consistently greater when *isotonic saline* solution was used than with hypotonic saline and either isotonic or hypotonic *glucose* solutions. The explanation for this may lie in the fact that isotonic saline diffuses only in the 12 odd liters of extracellular fluid, whereas the water of glucose solutions, after metabolism of the sugar, diffuses rapidly in the 50 liters of total body water, hence there is less net dilution effect on the plasma.

Our time is running short, and we have one more case that we would like to present. Go ahead, Dr. Cámara.

DR. CÁMARA: I shall try to be brief and mention only the pertinent facts in this case.

This patient was J. S., a 68 year old housewife who came to the hospital because of gradual enlargement of the abdomen of four months' duration and anorexia. Diagnostic studies revealed the abdominal mass to be a nonfunctioning hydronephrotic left kidney with several calculi in it. Nephrectomy was delayed because of her poor clinical status, with anorexia, nausea, and vomiting. Gastric suction was instituted on the twelfth hospital day and continued through the seventeenth day. The amount of gastric suction totaled 5,460 ml. during those six days when no electrolyte replacement whatsoever was given. She grew progressively weaker and apathetic and in the evening of the seventeenth hospital day she went into deep coma following convulsions. She was in this state when she was transferred to the Metabolic Unit on the eighteenth day. A presentation of the water and electrolyte data on her will show her progress more vividly than words can describe. (See table 2.)

Of particular interest in this table of data are the extreme degree of hyponatremia and hypochloremia that existed when we first saw her. This severe chemical imbalance undoubtedly was responsible for the coma, for following the first two infusions consisting of 1000 ml. of 0.45 per cent sodium chloride (with 2 Gm. of ammonium chloride and 2 Gm. of potassium chloride) and 1000 ml. of 0.9 per cent sodium chloride, she roused from her deep coma and started to respond. The following day after more electrolyte replacement she was sitting up in bed reading her get-well cards.

The intravenous fluids administered to this patient were partitioned into isotonic solutions and plain water, isotonicity being calculated on the basis of sodium chloride and ammonium chloride content of the fluids administered, as in the case of the data on the preceding patient. In other words, 1000 ml. of 0.9 per cent sodium chloride was listed as 1000 ml. of isotonic solution (as was 1000 ml. of solution containing 0.45 per cent ammonium chloride), whereas 1000 ml. of 0.45 per cent sodium chloride was considered to be 500 ml. of isotonic solution and 500 ml. plain water. Except for two liters on the eighteenth day and one liter on the twentieth day, of 0.9 per cent sodium chloride, all the sodium replacement in this patient was carried out with 0.45 per cent sodium chloride.

TABLE 2.—*Fluid and Electrolyte Data on Patient J. S., 68, F.*

	Surgical Floor						Metabolic Unit					
Hospital Day	12	13	14	15	16	17	18	19	20	21	22	23
Fluid intake, ml.												
(1) Oral	100	0	290	600	0	110	0	430	2140	1330	2370	2090
(2) I.V.												
(a) Isotonic	0	0	0	0	0	0	4000	2000	1500	0	500	0
(b) Plain H_2O	3000	4300	3000	4500	4500	6000	0	2000	500	2000	1500	2000
(3) Total	3100	4300	3290	5100	4500	6110	4000	4430	4140	3330	4370	4090
Body wt., Kg.	—	—	—	—	—	—	71.2	70.5	68.4	67.5	66.8	66.4
Urine												
(1) Volume, ml	1200	2650	3200	2520	2500	3200	4830	4240	3250	3100	3490	2970
(2) Sodium, mEq.	—	—	—	—	—	—	37.4	194	244	96.5	57.4	124
(3) Chloride, mEq.	—	—	—	—	—	—	51.3	211	266	106	62.5	139
(4) Potassium, mEq.	—	—	—	—	—	—	19.3	34.4	32.9	21.4	19.3	13.1
Gastric suction volume, ml.	1900	900	520	600	940	600	0	0	0	0	0	0
Electrolyte replacement in I.V.'s												
(1) Sodium, mEq.	0	0	0	0	0	0	462	308	231	0	77	0
(2) Chloride, mEq.	0	0	0	0	0	0	410	388	244	13	131	0
(3) Potassium, mEq.	0	0	0	0	0	0	107	80	13	13	54	0
Plasma values												
(1) Sodium, mEq./L.	—	—	—	—	—	—	103	—	128	—	136	136
(2) Chloride, mEq./L.	—	—	—	—	—	57.4	50.5	—	86.7	—	85.3	88.4
(3) Potassium, mEq./L.	—	—	—	—	—	—	2.7	—	3.9	—	3.7	4.7
(4) CO_2C.P., mEq./L.	—	—	—	—	—	—	31.0	—	25.0	—	21.4	28.2
(5) Sp. gravity	—	—	—	—	—	—	1.0214	—	1.0231	—	—	1.0242
(6) Osm. pressure (mOsm./L.)	—	—	—	—	—	—	103	—	136	—	—	147
Blood urea N, mg.%	—	—	—	14	—	15	15	—	9	—	—	12

Note that the initial plasma specific gravity on the day she came to the Unit (eighteenth hospital day) was low, and despite the use of hypotonic (half-strength) sodium chloride solutions, the remaining functioning kidney was able to effect correction of concentration, correction of pattern, and correction of volume of the extracellular fluid (rapid weight loss of 4.8 Kg. in five days). As soon as she was gotten into optimal condition a few days later, a successful nephrectomy was done.

DR. SCHEMM: We have had our best results results in correcting hyponatremia and/or hypochloremia by giving a sufficient amount of electrolytes and at the same time an adequate amount of plain water, as these two cases demonstrate. We have not seen the extra plain water interfere with correction of pattern or induce signs or symptoms of so-called water intoxication.

When we have used hypertonic (2 or 3 per cent) sodium chloride solutions we have found them sometimes rapidly effective only in improving pattern defects, but disadvantageous as compared to isotonic, or even hypotonic solutions, in that the hypertonic solutions do not allow for correction of the usually coincident and more important plain water deficits. In our experience, hyponatremia does not always indicate dilution of the extracellular fluid because, paradoxically enough, we have seen hyponatremia coexist with a high specific grav-

ity of the plasma, and we have seen it corrected by the use of hypotonic solutions (with regard to sodium) with coincident return of plasma specific gravity to normal values.

Summary

In this discussion of some of the points that have interested us in the correction of electrolyte deficits in cardiovascular-renal disease, we briefly reviewed the salt-losing syndrome in terminal nephritics and in hypertensives with advanced renal damage, and incidentally delved into the concepts of edema formation as we discussed its opposite mechanism. We found ourselves drawn into a discussion of potassium metabolism in the process, touching on the subject of "potassium losers." Next in the panorama of this multifaceted problem came the management of edematous patients who developed hyponatremia on the diuretic regimen (without losing their edema) or who became mercurial fast in "midstream"; i.e., after losing about half their edema. Under such dire circumstances, we showed how sodium chloride might be used to good advantage.

The promising use of corticotropin (ACTH) in hopelessly resistant cases of cardiac edema or in near-terminal severe cases of myocardial insufficiency, with incidental correction of a coexisting hyponatremia (accomplished without the use of sodium supplements) was described. Finally, we discussed in detail our use mainly of *hypotonic* solutions of sodium salts in correcting *concentration* as well as *pattern* and *volume* disturbances of the extracellular fluid in cardiovascular-renal patients who develop serious gastrointestinal and surgical complications. We emphasized that in such patients we have obtained the best end results with mainly hypotonic and isotonic, rather than hypertonic salt solutions. With this form of electrolyte replacement therapy, we have seen more floating on water and less drowning in brine!

CLINICAL PROGRESS

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Clinical Study and Treatment of Varicose Veins

By HUGH MONTGOMERY, M.D., AND HAROLD A. ZINTEL, M.D.

IN GENERAL, the common management of varicosities of the lower extremities often leaves much to be desired. There appears to be too little understanding of the basic physiologic disturbances, too much delay in initiating definitive therapy, and altogether too frequent use of inadequate and even harmful therapeutic measures. Perhaps the lack of interest in the patient with varicose veins is partially due to the fact that seldom do varicosities shorten the patient's life or cause death. It is possible that the many tests for varicosities and the multiple nomenclature associated with some of these tests have discouraged a better general understanding of this subject. The symptoms of varicose veins and their complications (vague discomfort, pain, edema, dermatitis, ulceration and hemorrhage) do produce considerable disability over many years and are real problems to the patient. The high incidence of varices in the general population demands that all general practitioners as well as the surgeon and vascular specialist have a basic understanding of these problems. We should have a sound idea of the underlying physiologic disturbances and the most useful therapeutic measures. The proper diagnosis should be made early, and the type of therapy which will give the patient the greatest relief and promise for the future should be promptly instituted.

From the Vascular Section of the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania and the Department of Surgery, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

It is the purpose of this paper to present briefly the normal and abnormal anatomy and physiology of the major veins of the lower extremity, to accent the importance of venous and opposing pressures in the problem, to outline a simple method of testing for the various types of varicosities, and to describe the types of therapeutic measures used.

A varicose vein by definition is an enlarged and tortuous vein. The present discussion is limited to the major venous channels of the lower extremity and includes neither the small, isolated, superficial cutaneous varices, the so-called spider web nevi, nor arteriovenous fistulas. The problem is with veins having incompetent valves ("incompetent veins"), regardless of whether or not the veins are as yet enlarged or tortuous. Because of valvular incompetence the veins will eventually become enlarged and tortuous, and other segments of the same vein and/or adjacent veins will also become involved.

ETIOLOGY

The three common causes of valvular incompetence and varices are as follows. (1) Hereditary: It is not unusual to find that several individuals in each of several generations of a family have marked varices. (2) Occupational: The exact role of an occupation requiring standing for prolonged periods of time is not known. It is assumed, however, that prolonged standing, with or without moving, produces varices more quickly in the individual prone to develop varices than in an individual not prone to the development of

arices. (3) Inflammatory: Inflammation as roduced by thrombophlebitis may destroy he valves or render them incompetent. hrombophlebitis occludes veins temporarily, nd though the occlusion is in time relieved by ecanalization, the valves remain incompetent. his also occurs following the injection of clerosing agents. One must keep in mind the distinction between a vein having incompetent alves, which for practical purposes is synonymous with the term "incompetent vein," and the "occluded vein," a vein that has lost its lumen.

Normal Physiology

There are no valves of the vena cava and, more frequently than not, none of the common and external iliac veins. According to Basmajian[1] only 1 to 7 per cent of patients have a valve in the common iliac vein and only 24 per cent in the external iliac vein. The majority of individuals (67 per cent) have their most proximal valve in the common femoral vein immediately above the entrance of the great saphenous vein. There is great variability of the number of valves found in the major venous channels (table 1). When a normal individual stands erect the effective hydrostatic pressure in the veins at any level in the leg is equal to a column of blood extending up to the right heart.[2-5] In most individuals the proximal valve in the common femoral vein supports a column of blood extending up to the level of the right heart. There may be no other valve in the common femoral vein (table 1).

When a normal individual is in the supine position the venous pressure in any vein of the leg is roughly that of a column of water 15 cm. high.[6] The effective osmotic pressure of the plasma is some 20 cm. of water. This increases somewhat on prolonged standing because of ultrafiltration into tissues.[7] The hydrostatic pressure in the tissues in the leg in the supine position is something under 10 cm. of water.[8] On prolonged standing this increases little in the subcutaneous areas, but may increase in muscle to some 50 cm. of water. In the average individual standing still, the venous pressure just above the ankle

Table 1.—*Number of Valves in Leg Veins*

	No. of Valves
Femoral	1 to 5
Popliteal	1 to 4
Great saphenous	12 to 18
Short saphenous	9 to 10
Posterior tibial	8 to 20
Anterior tibial	about 11

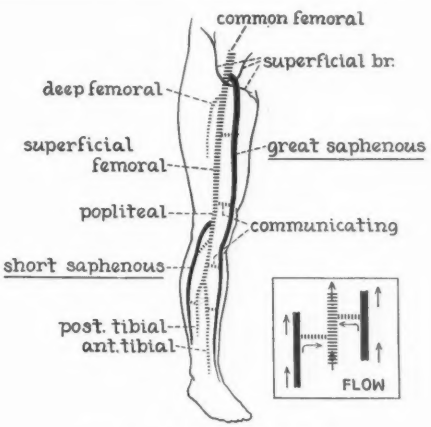

Fig. 1. Schema of veins of leg.

is equivalent to some 135 cm. of water (table 2). The pressures in the deep and superficial veins are about the same. Forced expiration with the epiglottis closed increases pressure by 50 cm. of water to make the total pressure some 185 cm. of water. Thus under the circumstances described or in an individual coughing, sneezing or straining, the venous pressure may be as high as the brachial artery pressure of 185 cm. of water (137 mm. Hg). Asmussen, Christensen, and Neilsen have estimated that 500 cc. of blood may pool in the legs of normal persons standing quietly.[9] On walking, the milking action of the muscles on the deep veins becomes effective, and the pressure in the veins at the level of the ankle is almost immediately reduced to some 70 cm. of water.[2-5, 10] Because the action of the muscles on normal veins with competent valves propels the blood toward the heart and tends to reduce venous pressure, it is referred to as the action of the "venous heart."

A simplified schema of the venous blood flow of the lower extremity is shown in figure 1.

The flow is normally upward and inward toward the common femoral vein, upward in the popliteal, superficial femoral, long and short saphenous veins and inward through the communicating veins. The blood flow of a cross section of the leg has been described as being similar to the cross section of a wheel with the blood flow inward through the spokes to the hub. Only below the ankle level can venous blood normally flow both inward toward the deep vein and outward toward the skin.

The superficial veins of the legs are poorly constructed to withstand marked increases in pressures for very long because they do not have strong fascia and muscle tissue support. This probably explains why primary varices, or varices of the superficial vessels are those most frequently encountered. Valvular incompetence of the deep veins with secondary varices of the lower superficial leg veins occurs most frequently following deep thrombophlebitis.

After elevation and then dependency of the leg, the normal rate of filling of its superficial veins is slow because refilling is by arterial blood flow through the capillaries. The normal filling time in the veins of the calf is usually considered to be 30 or more seconds. It may, of course, be lengthened by vasoconstriction or shortened by vasodilatation such as occurs in hot weather. When the valves are incompetent the filling time of the veins is usually between 2 and 10 seconds. Less than 30 seconds is considered to be a definitely abnormal filling time (fig. 2).

Abnormal Physiology

Primary varices, those of the long and short saphenous veins, represent the most frequently encountered type of varices in clinical practice. Their first appearance is often in the thigh or upper leg. Varices of the short saphenous vein are encountered less frequently than varices of the long saphenous system. In the development of primary varices of the long or short saphenous veins, continued excessive venous pressure and/or inherently weak valves and the lack of strong supportive perivascular tissue produces the incompetence of the proximal valve of the vein. With the development of incompetence of a valve the next most distal valve is subjected to a greater venous pressure, and it becomes more susceptible to becoming incompetent. Eventually the valves of the entire vein may become incompetent and the vein dilated and tortuous. As previously stated, occasionally the valves of a perforating or communicating vessel (usually in the region of the low thigh) become incompetent. When this is the case the first evidence of a varix may be a dilated isolated segment of the saphenous vein sometimes referred to as a "blowout." Occasionally, valves of the saphenous vein above and below the "blowout" may be competent. The femoral

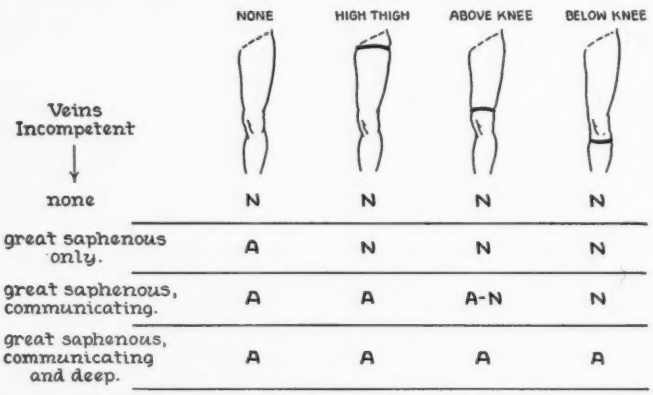

Fig. 2. Filling time of veins below a tourniquet level. N: normal filling time of 30 seconds or more. A: abnormal filling time of less than 30 seconds.

vein down to that point may have incompetent valves.

Postinflammatory or secondary varices usually follow old deep thrombophlebitis and usually appear as collateral channels first in the lower leg and ankle region and frequently are confined to the lower leg. Patients who develop such secondary varices usually give a history of having had old deep thrombophlebitis, or milk leg, three or more years prior to the development of visible varices although the varices may appear as early as one year and as late as 20 years after the phlebitis. The patient will usually, but not always, give a history of having had phlebitis following operation, delivery, trauma or severe infection. In a series of 246 cases reviewed by Ochsner and his co-workers, 24 per cent of the patients had none of the previously mentioned conditions, and 4 per cent of the patients were considered to have phlebitis resulting from varicosities.[11] The valves of the deep venous system, superficial femoral and popliteal veins are destroyed as previously described. Since the hydrostatic pressure is greatest in the most dependent portion of the leg, it is the veins in that part that develop varices first. (It is, of course, possible for an individual to have primary varices and then develop secondary varices either by extension or by reason of further valvular incompetence resulting from deep or superficial phlebitis.)

The blood flow through varices may actually be reversed when the individual stands.[12] This can be demonstrated by injecting radiopaque material proximally in a varix and then demonstrating a downward or peripheral migration of the radiopaque material by serial x-ray films. The lack of competent valves and probable reversal of blood flow indicate that the patient would be better off with these abnormal vessels eradicated, provided there is evidence of adequate collateral venous return.

In the patient with varices the venous pressure in the supine position and that on quiet standing can, for practical purposes, be taken to equal these pressures in the normal.[13] *Marked pressure differences between those having normal and those having abnormal veins are apparent only when the subjects walk.* In the presence of varices of the primary type the venous pressure is slightly reduced, but is not reduced to a normal value[3] on walking. When secondary varices exist there is no reduction in pressure on walking[2, 4, 10, 14, 15] (table 2). It is undoubtedly the abnormally high walking venous pressure that leads to sensations of tightness, pain, edema, dermatitis, and ulceration of the leg. Patients with primary varices and especially those with secondary varices have venous hypertension when walking. Treatment should, therefore, be directed toward reduction of the walking venous pressure. When the incompetent saphenous vein of an individual with primary varices is occluded by digital pressure or tourniquet, the venous pressure is reduced by walking to some 70 cm. of water, a normal reduction. One would therefore expect obliteration or ligation of the long saphenous vein to restore the normal pressure relationship in patients with primary varicosities of the long saphenous vein, and this is the case. As previously stated, it has been estimated that a

TABLE 2.—*Pressures (Average, Various Authors) in Superficial Vein of Ankle*

	cm. H_2O	mm. Hg
Normal subject supine	15	11
Normal subject leg elevated	0	0
Normal subject standing still*	135	100
Normal subject standing still with forced expiration†	185	137
Normal subject walking with or without tourniquet	70	52
Primary varices, subject supine	15	11
Primary varices, subject standing still	135	100
Primary varices, subject walking	95	70
Primary varices, subject walking with tourniquet	70	52
Postphlebitic, subject supine	15+	11+
Postphlebitic, subject standing still	135+	100+
Postphlebitic, subject walking	135+	100+
Postphlebitic, subject walking with tourniquet	135+	100+
Effective osmotic pressure of plasma	20	15

* 120 cm. to right atrium.

† 50 cm. H_2O produced by forced expiration against closed glottis.

normal person standing still "pools" approximately 500 cc. of blood in the legs. The amount of pooling in patients with large varices must be considerably in excess of this amount.

Mayerson and associates[13] believe that an increased blood volume explains the slight increase in supine resting venous pressures observed in some patients with varices (table 2). Chapman and Asmussen[16] found that cardiac output and systolic pressure were decreased after ligation of varicosities. In the postphlebitic leg the valves of the deep veins are usually incompetent and the valves of the superficial veins may have also become incompetent. The standing pressures in such veins are moderately in excess of that of normal veins and of primary varices. Walking with and without tourniquets fails to decrease this pressure, and may increase it[4] presumably because the tourniquet obliterates only the superficial veins and the deep veins are either incompetent or occluded.

Examination of the Patient with Varices

The physical examination of the patient with varices does not require a special knowledge of the complicated terminology associated with the many tests. The necessary equipment consists of (1) a place for the patient to lie down, (2) a watch with a second hand, (3) a pen or a marking pencil, and (4) a tourniquet of soft rubber tubing at least three-eighths of an inch in diameter. The clothing is arranged so that the entire lower extremities are exposed. The legs are examined for evidence of scars, erythema, edema, pigmentation, ulcers, any active phlebitis, arterial pulsations and any severe blanching on elevation. With the patient standing, the course of the more conspicuous veins is marked on the skin. The tension of these vessels is noted by simple palpation. Less conspicuous vessels may often be demonstrated after warming the patient, or by having the patient strain by forced expiration with the glottis closed in order to increase the venous pressure. The remainder of the examination consists of observing the rate of filling of the varices with and without the use of a tourniquet.

With the patient supine, one leg is raised and supported at a 45 degree angle for 30 seconds. The patient quickly assumes the standing position with his weight equally distributed on both feet, and the filling time of the varices is noted. A filling time (without tourniquet) of less than 30 seconds indicates abnormal filling (fig. 2). The maneuver is repeated, again starting in the supine position, with a tourniquet placed around the thigh at a level approximately 6 cm. below the inguinal fold in the midline and the patient quickly assumes the upright position. The tourniquet should prevent reflux blood flow through an incompetent long saphenous vein. Moderate tourniquet pressure will easily occlude the superficial veins. (The deep veins will not be occluded unless the tourniquet is very tight.) When the varix has filled to what is thought to be a tension equivalent to the tension observed when the patient was standing without a tourniquet, the vein is said to be filled and the filling time is noted. The maneuver is repeated, applying the tourniquet at the midthigh, lower thigh, upper leg and at levels down to the lowest varices.

In the case of the simplest, most frequently encountered type of varices, primary varices of the long saphenous vein, the tourniquet at high thigh will considerably delay the venous filling to 30 seconds or more, and one can assume that the communicating veins and the deep veins are competent (fig. 2). If, however, with the same use of the tourniquet, there is little or no delay in filling, an incompetent communicating vein is present below the level of the tourniquet. Application of the tourniquet at successively lower levels will demonstrate the site of this and perhaps other incompetent communicating veins (fig. 2). A tourniquet above the level of any incompetent communicating vein will not prevent the contribution of this incompetence to the filling of a varix of the lower leg, but a tourniquet applied just below it will. Frequently palpation of the thigh in the area of an incompetent communicating vein will reveal a "soft spot" in the tissues which indicates the point of emergence of the incompetent communicating varix into the saphenous vein in the subcutaneous fat.

This point of emergence is usually slightly tender. Digital pressure on the vein in this area will produce a conspicuous delay in the filling time of the varices if it is the only, or the lowest incompetent communicating vein. Of course, a tourniquet at no level will delay filling of the varices if there is incompetence of the valves of all three systems of veins, the superficial, deep and communicating (fig. 2). An incompetent short saphenous vein is distinguished from an incompetent long saphenous vein by the posterior position of the former in the calf and by the fact that firm pressure by the finger in the lower portion of the popliteal space will delay its filling.

In summarizing the information (fig. 2) obtained as previously described, one can determine whether (a) all the veins have competent valves, and, if there is incompetence, whether it is of (b) the long saphenous vein, (c) the communicating veins, (d) the deep superficial femoral and popliteal veins, (e) combinations of the former, and (f) the short saphenous vein.

Before surgery is considered for the treatment of varicosities it is necessary to demonstrate that the deep veins are not occluded. This is done by firm bandaging of the leg from the ankle to the groin with an elastic or rubber bandage and having the patient walk for at least five minutes.[17] The bandage prevents blood flow in the superficial veins but not in the deep veins or arteries. If the deep veins are occluded by disease the patient will, with such bandaging, complain of the severe pain of ischemia while walking. If there is evidence of occlusion of the deep veins, then extensive surgical excision of the varices is contraindicated. A single tourniquet will not take the place of such bandaging because flow may take place around an occlusion of a deep vein by way of communicating and superficial veins.[18]

Surgical Treatment

In general the best treatment of primary varices of the long and short saphenous vein is by surgical means. In the past we tried (1) injections of sclerosing agents, (2) ligation of the long and/or short saphenous veins, (3) combinations of ligation and sclerosing agents, (4) ligation of incompetent communicating veins, and (5) multiple ligation. At the present time it appears that vein stripping is the most useful method. The method of vein stripping was used a number of years ago and then for some unknown reason fell into disrepute. It has been more effective, however, in the treatment of varicosities than have any of the previously mentioned methods or combinations of methods which are described above. According to a recent review of the literature by Fenney,[19] the injection treatment of varices is followed by recurrence of varices in 57 to 98 per cent of the individuals so treated, and combined ligation and injection in 15 to 96 per cent of the individuals. Apparently the longer the individuals are followed the higher is the recurrence rate.

Vein stripping accomplishes in one operation more than could be hoped for by any other method or combination of methods. The data reviewed by Fenney indicate that great saphenous ligation, ligation of the other superficial veins at the saphenofemoral junction, and stripping of the great saphenous vein are associated with recurrences in from 2 to 7 per cent of properly selected patients with primary varices. Stripping abolishes all of the communications to the veins stripped and does more than abolish the communicating vein or veins demonstrated by the examiner. It leaves no segments of superficial and communicating veins to become dilated and tortuous after a collateral circulation has been established. It does not leave an occluded vein which can later become recanalized. The disadvantages of vein stripping are that patients are asked to remain in the hospital until the fifth postoperative day and that some patients may have slight transient edema of the ankle region for several weeks following operation.

For superficial primary varices and varices of the long and short saphenous veins, stripping of the involved vein or veins is advocated provided the deep veins of the leg are not occluded, as demonstrated by the compression bandage test previously described. For stripping of the long saphenous vein the patient is

placed supine on the operating table with the lower abdomen and both extremities completely exposed. The involved leg is then completely prepared with an antiseptic agent. The foot and the toes are wrapped in a sterile towel, but the ankle region is left exposed. The saphenofemoral area is then exposed, as for a saphenofemoral ligation, through a vertical incision approximately 2.5 inches long. The long saphenous vein is identified and divided between Kelly clamps approximately an inch and a half below the saphenofemoral junction. A chromic no. 0 ligature with a half knot is placed loosely around the vein distal to the clamp on the distal end of the severed vein. After applying hemostats to the cut edges of the vein, the small end of a flexible shafted intraluminal stripper is easily introduced into the lumen as the clamp is released. With gentle probing of the vein the stripper is easily introduced to just below the level of the knee. Not infrequently it can be inserted to the level of the ankle. When the tip of the stripper has been advanced as far as possible, a half inch incision is made over the tip of the stripper and the vein is exposed and divided. A clamp is placed on the distal end of the vein. The hemostats are removed and the stripper is advanced until the large olive tip of the proximal end of the stripper engages the proximal end of the vein segment. The catgut ligature is then tightened and the knot completed around the vein and the shaft of the stripper. The vein segment is then removed by firm traction on the distal end of the stripper. The skin overlying the stripped segment is then compressed with the spread fingers of both hands over a folded towel. Usually two to five minutes of such compression will control the hemorrhage from the ruptured communicating and collateral vessels. If the entire saphenous vein has not been removed, the procedure is then repeated attempting to remove the remaining segment of vein to the ankle. Occasionally the long saphenous vein is exposed just anterior to the medial malleolus and the vein is stripped upward instead of downward. Sometimes this is the only possible means of stripping the veins. Finally the uppermost, remaining portion of the saphenous vein is excised together with its various branches, and the saphenous vein is ligated flush with the surface of the common femoral vein. The entire leg is moderately compressed with an elastic bandage extending from the toes to the groin. Ambulation is allowed on the evening of the day of operation. On the fifth day after operation the sutures are removed, the use of elastic bandages is discontinued and the patient is allowed to go home with no restriction of ordinary activities. In individuals having very tortuous varices it may be impossible to strip the veins and multiple ligations may be necessary. This difficulty favors the early treatment of varices.

For the patient with a single or with several demonstrated communicating veins producing a blowout of a very short segment of the saphenous vein, excision of the segment and of a portion of the communicating vein will frequently suffice. This assumes, however, that the patient probably does not have nondemonstrable incompetent communicating veins. For this reason we frequently advise stripping of the upper or even of the entire long saphenous vein even though only a short segment of the saphenous vein is involved. Varices of the short saphenous vein are treated in a similar manner. The initial incision is made transversely in the lower popliteal space.

In other hands good results have been obtained, without stripping, by multiple ligations and excisions of segments of incompetent superficial and communicating veins. When performed in numerous stages under local anesthesia the procedure has the advantage of keeping the patient ambulatory.[20] It is doubtful, however, whether the multiple operations on an ambulatory basis actually save the patient much time or expense.

In general, it is best to inform patients preoperatively, especially those with primary varicosities, that operations cannot cure the underlying cause of varices. When varices develop because of an inherent vessel or valvular weakness, it is entirely possible that varices can develop in other vessels. The patient should know that operation will not eliminate all of the dilated veins of the legs when such dilated

veins are tributaries of the long or short saphenous trunks. They should understand that the incompetent veins causing the dilatation of these tributaries must be eradicated by operation. Any few remaining dilated vessels are dealt with very satisfactorily after stripping by injection of 1 cc. of sodium morrhuate or similar sclerosing agents. Usually the very small or "intracutaneous" varices are not treated by excision, and can be lessened by individual injections if the patient objects to cosmetic defect. Patients should know that the elimination of these tiny "intracutaneous" varices is very time consuming. The patient can be told that intelligent surgery will prevent the more serious symptoms and complications of varices. With proper treatment he can live comfortably, but he is not actually cured of his tendencies to develop varices.

For the patient with incompetent deep veins, popliteal and superficial femoral, we have usually employed elastic support, rest, and occasional grafting of ulcers but have occasionally used the venous ligation of Linton.[21] He has advocated ligation of the superficial femoral vein and stripping of the long and short saphenous veins if varicosities are demonstrated in them. For this operative procedure the entire leg is prepared as previously described. The saphenofemoral junction is exposed as well as the superficial femoral vein below the profundal vein. Number 8 soft rubber catheters or small pieces of rubber tubing of similar size are placed around the most proximal portion of the long saphenous vein and the superficial femoral vein just below the profundal branch to act as tourniquets. With the aid of a water manometer such as is used to measure spinal fluid pressures, a three way stopcock, saline solution containing 10 mg. of heparin per 100 cc. and an 18 gauge needle, the venous pressure is taken in the superficial femoral vein distal to the occluding catheter. The pressure reading is observed after the more proximal portion of the superficial femoral vein and the long saphenous veins have been temporarily occluded for several minutes with the rubber catheters. If the venous pressure is 30 cm. or more of water as measured from the level of this vein, only the superficial femoral is ligated and interrupted. If the long or short saphenous veins are varicosed, their stripping is delayed for two or three months to allow time for venous collaterals to form. Unfortunately this operation and the popliteal vein ligation of Bauer[22] do not reduce walking pressure in the veins of the leg,[14, 23, 24] and the end results are far short of those obtained following surgery for primary varicosities. Rest, elevation and elastic support are frequently essential adjuncts to surgical therapy in secondary varices.

Summary

The widely different kinds of varices are easy to differentiate if the underlying anatomy and physiology are understood. Appropriate therapy is wholly dependent upon this understanding. Surgery is a reasonably definitive therapy of primary varices, but secondary varices usually require rest, elevation and elastic support.

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ABSTRACTS

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PATHOLOGIC PHYSIOLOGY

Van Bogaert, A., Van der Henst, H., Van Genabeek, A., and Vandael, J.: Pulmonary Arterial Pressure and Oxygen Content of Pulmonary Artery. Clinical and Experimental Study. Arch. mal. coeur **46:** 1 (Nov.) 1953.

The authors summarize current ideas concerning the relationship between oxygen and carbon dioxide content of the pulmonary arterial blood (or of the alveoli) and pulmonary vascular resistance. According to the most reliable studies, a decrease of vascular resistance (vasodilation) can be due to: (a) diminution of oxygen or increase of carbon dioxide in the blood of the pulmonary artery; or (b) increase of oxygen in the alveoli. On the contrary, an increase of vascular resistance (vaso-constriction) can be due to: (a) increase of oxygen or decrease of carbon dioxide in the blood of the pulmonary artery; or (b) decrease of oxygen in the alveoli.

Following this conception, left-to-right shunts should increase the oxygen content of the pulmonary artery and should present evidence of vasoconstriction. A review of 105 cases from the literature showed increase of pulmonary systolic pressure in 78, of diastolic pressure in 48. As a conclusion, it was noted that no close relationship could be ascertained.

The authors perform animal experiments by creating a carotid-jugular fistula, or a carotid-jugular transfusion between two animals. Changes of pulmonary arterial pressure seemed related to the mechanical increase of venous return, not to the oxygen content of the blood. On the other hand, the changes of pulmonary pressure were extremely variable, and this was accepted as evidence of a pulmonary vascular reaction superimposed on, or counteracting, the mechanical response.

LUISADA

Rakita, L., and Sancetta, S. M.: Acute Hemodynamic Effects of Hexamethonium in Normotensive Man. Circulation Research **1:** 499 (Nov.), 1953.

The effect of intravenous hexamethonium bromide was investigated in 12 normotensive human subjects in the steady state. Changes in cardiac output were variable, and the heart rate was generally increased. There were borderline significant percentile decreases in brachial and pulmonary artery pressure, pulmonary and total peripheral resistances, and left ventricular work. There was a marked individual variation in dose response. The data indicate that hexamethonium lowers arterial pressure in normotensive man primarily by diminishing total peripheral resistance rather than cardiac output.

MAXWELL

Goodale, W. T., and Hackel, D. B.: Myocardial Carbohydrate Metabolism in Normal Dogs, with Effects of Hyperglycemia and Starvation. Circulation Research **1:** 502 (Nov.), 1953.

Myocardial metabolism of Nembutalized intact dogs was studied by means of the coronary sinus catheterization technic.

Oxygen, glucose, lactate and pyruvate were extracted by the heart in direct relation to the arterial level of each substance and independently of the others. Total myocardial utilization of each metabolite was the product of two independent variables: (a) coronary blood flow, and (b) coronary A-V differences. Under ordinary conditions, glucose

extraction was sufficient to provide the major potential source of fuel for myocardial oxidative energy. Pyruvate and lactate showed a high myocardial extraction coefficient, but the low arterial levels at rest prevent these metabolites from accounting for more than 50 per cent of the total myocardial energy requirements. During starvation, the heart probably derived its energy from fat, as indicated by a myocardial respiratory quotient near 0.70 and a low myocardial carbohydrate extraction.

MAXWELL

Morris, G. C., Jr., Moyer, J. H., Snyder, H. B., and Haynes, B. W., Jr.: Vascular Dynamics in Controlled Hypotension: A Study of Cerebral and Renal Hemodynamics and Blood Volume Changes. Ann. Surg. **138:** 706 (Nov.), 1953.

The use of controlled hypotension in surgery has gained rapid momentum during the past five years in Britain and on the European continent. This followed the work of earlier authors who reduced the blood pressure by blockade of the sympathetic nervous system with high spinal anesthesia. The use of ganglionic blocking agents to obtain a similar degree of hypotension has further increased the applicability of the method because of its simplicity. Since there has been a paucity of reported studies regarding the altered vascular dynamics, particularly in such critical vascular beds as the brain and kidney, the current investigation is concerned primarily with measurements of cerebral blood flow and cerebral oxygen consumption in a group of surgical patients with marked hypotension induced by hexamethonium.

Hexamethonium chloride was administered as a continuous infusion (500 mg. of hexamethonium per 1000 cc. 5 per cent glucose in water) to the unanesthetized, horizontally supine patient. The patients were not anesthetized in order that the disturbances in renal function could be immediately recognized, thus increasing the safety factor in these initial studies. Continuous mean blood pressure recordings were made from a mercury manometer connected to a needle inserted in the femoral artery.

The following conclusions were arrived at and indicated a significant decrease in cerebral blood flow following marked depression in the mean blood pressure in spite of a decrease in cerebral vascular resistance. Cerebral oxygen consumption was only slightly decreased due to a more complete extraction of oxygen from the blood flowing through the brain. Initially, glomerular filtration rate and renal plasma flow were both depressed. However, after two to three hours of maintained hypotension, renal plasma flow returned to control levels, whereas glomerular filtration rate remained depressed. Hexamethonium-induced hypotension decreased urine formation.

Blood volume studies were done employing 5 cc. of radioactive iodinated human serum albumin (10 microcuries per cc.) and the increases in these findings were due predominantly to an increase in plasma volume. The authors conclude that there appears to be little danger of cerebral or renal anoxia in a supine patient with a mean blood pressure as low as 55 mm. Hg when employing hexamethonium-induced controlled hypotension.

DENNISON

Kowalski, H. J., and Abelmann, W. H.: The Cardiac Output at Rest in Laennec's Cirrhosis. J. Clin. Investigation **32:** 1025 (Oct.), 1953.

Patients with Laennec's cirrhosis often have a short circulation time, and warm extremities, wide pulse pressure, and capillary pulsations in the nail beds. These findings suggest an elevated cardiac output and an increased peripheral blood flow.

Observations are reported on 22 patients with apparent cirrhosis of the liver as determined from the history of alcoholic intake and laboratory evidence of chronic disease of the liver. Patients were selected who had no evidence of coexisting heart disease. Eight of the group had either ascites or peripheral edema, or both. Eleven had Laennec's cirrhosis without fluid retention. All had abnormally high Bromsulphalein retention. The findings indicate that the resting cardiac output was elevated in one-third of the patients and was associared with normal blood pressure, low peripheral vascular resistance, and a large stroke volume. The elevated cardiac output in this group of patients was out of proportion to the oxygen consumption. This finding indicates a decreased arteriovenous oxygen difference. The patients had all received thiamine in ample amounts and it does not seem likely that beriberi was present.

Evidence is presented for the suggestion that the increased blood flow is due to dilatation of the peripheral vascular bed.

Eight patients had a prolonged Q-T interval. Four of these eight had a high cardiac output. The other electrocardiograms were normal.

WAIFE

Yu, P. N. G., Lovejoy, F. W. Jr., Joos, H. A., Nye, R. E. Jr., and Simpson, J. H.: An Unusual Case of Massive Pericardial Effusion with Hemodynamic Studies. Ann. Int. Med. **39:** 928, (Oct.), 1953.

Despite clinical and pathologic investigations in many patients with pericardial effusion, few such patients have been studied by cardiac catheterization. It is the purpose of this manuscript to present clinical and hemodynamic observations on a patient with massive pericardial effusion. Cardiac output, intravascular and intrapericardial pressures, blood gas analysis, and other related clinical and laboratory findings are described before and after pericardial aspiration and six months following pericardiectomy. Hemodynamic studies were done

during the first pericardial aspiration, before and immediately after the second pericardial aspiration, and six months after pericardiectomy. These studies reveal improvement in the altered patterns basically recorded. The initially altered right atrial and superior vena caval pressures were lowered. There was an improvement in the stroke index and stroke volume. In addition, there was a decrease in the heart rate. Little or no improvement in the cardiac output resulted. Finally, the elevated pulmonary artery and "capillary" pressures observed during the postoperative cardiac catheterization reflect some impairment of the blood through the left side of the heart. It is quite likely that some interference with diastolic filling of the left ventricle existed, perhaps due to residual pericardial and/or myocardial scarring.

DENNISON

Petrakis, N. L., Masouredis, S. P., and Miller, P.: The Local Blood Flow in Human Bone Marrow in Leukemia and Neoplastic Diseases as Determined by the Clearance Rate of Radioiodide (I^{131}). J. Clin. Investigation **32:** 952 (Oct.), 1953.

Forty-three patients with a variety of malignant diseases and leukemia were studied by a radioisotope clearance technic using I^{131}. The clearance rates of the isotope through the marrow were found to be approximately the same as in resting muscle in 17 nonleukemic patients studied. The marrow clearance rates were increased in five cases of acute leukemia. However, in five of seven subjects with chronic myelocytic leukemia and in two instances of monocytic leukemia, the marrow clearance rates were within the normal range. Six of 10 patients with chronic lymphocytic leukemia had elevated clearance rates as did three out of four with multiple myeloma. The findings appear to demonstrate a selective increase in blood flow in the bone marrow in acute leukemia, in some cases of chronic leukemias and multiple myeloma, thereby suggesting a fundamental difference in the vascular bed of the marrow in the presence of this disease. There was no relationship between the clearance rate and the hemoglobin level, nor could a correlation be established between the bone marrow cytology or peripheral blood picture with the clearance rates.

WAIFE

Van Bogaert, A., Van der Henst, H., Van Genabeck, A., and Vandael, J.: Pulmonary Arterial Tension and O_2 Content of the Pulmonary Artery. Arch. mal. coeur **46:** 961 (Nov.), 1953.

In an attempt to determine experimentally the cause of pulmonary hypertension in congenital and acquired lesions shunting arterial blood into the venous circulation, the authors produced in dogs an end to end anastomosis between a carotid artery and a jugular vein. In a number of experiments pulmonary hypertension developed acutely in association with the augmentation of right ventricular output caused by the operation. Theoretically this would not be expected to occur because the pulmonary circulation can accommodate considerable amounts of shunted blood by reduction of resistance in its arterioles. Increase of the O_2 content of the pulmonary blood has by itself a feeble vasoconstrictive action which, however, is insufficient to oppose the vasoconstriction caused by the increase in blood flow. The authors conclude that some other, so far unknown mechanism, must be in operation which influences the reaction of the pulmonary vascular tree to a sudden overload in such a way, that pressure elevation results.

PICK

Sawyer, P. N., and Pate, J. W.: Electrical Potential Differences Across the Normal Aorta and Aortic Grafts of Dogs. Am. J. Physiol. **175:** 113 (Oct.), 1953.

Graft implantations were made into aortas and the potentials in recipient vessels were studied. When trauma was slight the intima became more negative with respect to adventitia. Severe trauma produced a positive intimal potential which was proportional to the extent and duration of the trauma. Fresh grafts had positive potentials. These are living tissues but show an injury potential. Freeze-dried grafts are not bio-electrically living tissues. When reconstituted they will serve as a satisfactory prosthesis but have no electrical potential. The intima can not be demonstrated and thrombosis does not take place.

OPPENHEIMER

PATHOLOGY

Bourne, G., and Cureton, R. J. R.: Haemochromatosis of the Heart. Lancet **6792:** 917 (Oct. 31), 1953.

A case is presented in which a patient with diagnosed hemochromatosis and no previous cardiac symptoms developed congestive heart failure and died within nine days of his initial cardiac complaints. At autopsy, the heart showed siderosis throughout with fatty infiltration of the right ventricle. It is suggested that the reason for the absence of previous symptoms was equal damage to both sides of the heart, with the result that there was no imbalance between the systemic and pulmonary circulations.

MAXWELL

Corsi, V., Sciacca, A., Sangiorgi, M., and Farulla, A.: Histologic Studies in Serial Sections of the Bundle of Paladino-His in a Case of Rare Type of Bundle Branch Block Present in a Syphylitic Subject. Acta cardiol. **8:** 509 (Fasc. 5), 1953.

Serial histologic sections of the conduction system are presented from a case with a typical electrocardiogram of right bundle-branch block. Alterations of degenerative type were seen with partial

invasion of the two bundle branches by connective tissue. The common bundle showed destruction of its right half above its bifurcation, while its left half was intact. The anatomic findings confirm, in the opinion of the authors, a hypothesis advanced previously by Condorelli. According to his views the fibers of the common A-V bundle are anatomically and functionally divided into two portions, each of which eventually forms after its bifurcation the right and left bundle respectively. It is therefore possible that a partial interruption of the common bundle may result in the pattern of bundle-branch block, without an actual lesion present in one of the bundle branches.

PICK

PHARMACOLOGY

Gruhzit, C. C., Freyburger, W. A., and Moe, G. K.: The Action of Veriloid on Carotid Pressoreceptors. J. Pharmacol. & Exper. Therap. **109:** 261 (Nov.), 1953.

The role of the carotid reflexes in the depressor response to Veriloid was investigated in dogs. Combined section of the vagi and of the carotid sinus nerves abolished the usual decrease in blood pressure and heart rate following the administration of Veriloid; either of these procedures alone, however, was ineffective. Following vagotomy, denervation of the carotid pressoreceptors without destruction of the chemoreceptors completely prevented the depressor response to the drug. Since Veriloid did not potentiate the depressor effect of submaximal electrical stimulation of the carotid nerves, it was concluded that the drug causes hypotension by sensitization of the stretch receptors, rather than by facilitation of central components of the reflex arc.

MAXWELL

Finnerty, F. R. Jr., and Fuchs, G. J.: The Veratrum Treatment of Toxemia of Pregnancy: A Controlled Study. Am. J. Obst. & Gynec. **66:** 831 (Oct.), 1953.

The following treatment schedule was used for the treatment of nonconvulsive toxemia of pregnancy: (1) Give intramuscularly the purified vera trum product mixed with 1 per cent procaine. (2) Record blood pressure and pulse every half hour. (3) Repeat the injection of Veratrum every hour, if necessary, whenever the blood pressure is over 140/90. (4) A gradual increase of dosage is recommended if no hypotensive effect is observed. (5) If nausea and vomiting occur, give 50 mg. of phenobarbital sodium intravenously. In 308 such cases, the intramuscular administration of purified Veratrum gave excellent results in 241 (78 per cent), and good results in 50 (17 per cent); there were no maternal deaths and five fetal deaths. Severe preeclampsia was treated alternately with veratrum and pentobarbital-magnesium sulfate in 100 patients. In the veratrum group, the average blood pressure decrease was 23.1 mm. Hg, in the pentobarbital group, the average blood pressure increased by 4.1 mm. Hg. Also, in the treatment of severe eclampsia, Veratrum was found to be superior to other methods of treatment.

SHUMAN

Silber, E. N., and Katz, L. N.: Coronary Dilators and Angina. J.A.M.A. **153:** 1075 (Nov. 21), 1953.

Drugs that dilate the coronary vessels are useful. It is essential to ascertain that such drugs do not divert blood from the coronary circuit by a disproportionate dilator action on the other systemic circuits. Drugs that increase coronary flow should not at the same time increase the metabolism or work of the heart. The term coronary insufficiency, as an expression of inadequate nourishment of the heart by its circulation, serves a useful purpose. However, the concept that coronary insufficiency is measured by angina pectoris is fallacious because of the fact that pain is analyzed in terms of the physiology of sensation, which is quite apart from factors having to do with coronary flow. Often, discrepancies in results between clinical evaluation of coronary dilators and animal experimentation are noted. In some cases experiments are to blame; sometimes the blame concerns the object of the study; in other cases the investigator. In studies of so highly a subjective ailment as angina, the need for repeated substitution with the so-called "double blindfold method" is apparent because many patients react readily to this "ceremony of therapy." These patients often show improvement regardless of what drug is used, even with placebos. The major source of error in clinical studies is bias, either conscious or unconscious on the part of the investigator. There may be little correlation between the ability of a drug to prevent electrocardiographic changes under stress and to prevent anginal pain. The authors do not believe papaverine, visammin, dioxyline phosphate, or pentaerythritol tetranitrate are of any use in the treatment of angina. They are currently working on the effects of estrogens on the anginal syndrome but have no report to make on this drug.

KITCHELL

Roth, O., Montano, G. M., Piccolo, J. A., Cavallaro, A. L., Sharkey, D., and Celentano, R.: Chlortetracycline (Aureomycin) in Prevention of Bactermia Following Oral Surgery. Arch. Int. Med. **92:** 485 (Oct.), 1953.

Twenty adult patients with organic heart disease due to various causes were treated with 2 Gm. of chlortetracycline (Aureomycin) daily in four divided doses on the day before, the day of, and the day after surgery. The last preoperative dose of 0.5 Gm. of chlortetracycline was given two hours prior to surgery to assure high blood levels at the time of

possible bacteremia immediately following extraction. Blood cultures taken before onset of therapy, immediately before and after surgery, half an hour later, 24 hours later, and four weeks later were sterile. The results obtained in this study give additional support to previously reported findings on 25 patients without heart disease, that chlortetracycline used prophylactically is successful in greatly reducing bacteremia following oral surgery. The fact that blood cultures of all patients with cardiac disease four weeks after surgery were negative and that none of these patients showed any signs of subacute bacterial endocarditis after careful history and physical examination strongly suggests the value of chlortetracycline in preventing detectable bacteremia, and in presumably preventing subacute bacterial endocarditis following oral surgery and most likely surgery in any contaminated area of patients with cardiac disease.

BERNSTEIN

Belsky, H.: Use of a New Oral Diuretic, Diamox, in Congestive Heart Failure, New England J. Med. **249:** 140 (July 23), 1953.

Diamox, a carbonic anhydrase inhibitor producing loss of bicarbonate, sodium, potassium and water, was used in 13 patients with congestive failure who were previously treated with digitalis, low-salt diet and mercurial injections. Eleven patients were kept free of edema on doses of Diamox of 0.5 Gm. daily together with the low-salt diet and digitalis. Eight patients were able to dispense with mercurial injections completely. The periods of observation ranged from one week to six months. Toxic effects of the drug consisted of paresthesias of the face and extremities and moderate to extreme drowsiness. These symptoms were encountered when the daily dose was 1 Gm. or more and became minimal when the dose was reduced to 0.5 Gm. daily. No evidences of hematopoietic or renal toxicity were encountered.

ROSENBAUM

Fisher, K., and Winsor, T.: Control of Vagal Cardiovascular Reflexes During Surgery Employing β-Diethylaminoethyl Xanthine-9-Carboxylate Methobromide. Anesthesiology **14:** 596 (Nov), 1953.

The authors studied the frequency and severity of vagal cardiovascular reactions (brachycardia and arterial hypotension) in 202 patients before, during and after surgery (194 chest operations and 8 abdominal operations) and in 88 nonsurgical patients undergoing medical treatment. All of the surgical patients received morphine, scopolamine and Seconal preoperatively. These patients were divided into four groups depending on subsequent medication: Group I (79 patients) received no additional medication; group II (55 patients) were given digitoxin, 0.8 or 1.2 mg. orally, 12 hours before operation; group III (27 patients) received methantheline bromide (Banthine), 50 to 100 mg. orally, one to two hours before operation; and group IV (41 patients) were given both digitoxin and methantheline bromide prior to surgery in the doses described. Anesthesia consisted of pentothal and curare for intubation and ether and oxygen or nitrous oxide and oxygen for maintenance. Operations for hiatus hernia and carcinoma of the esophagus caused a higher percentage of vagal cardiovascular reactions than found in any other types of surgical procedures in this series. The time of occurrence of the vagal reaction averaged 32 minutes after intubation and was associated most commonly with incision of the chest wall, rather than with intubation or hilar traction. The patients who received both methantheline bromide and digitalis (group IV) showed the lowest frequency of vagal cardiovascular reaction, while the highest incidence of such reactions was found in group I patients who did not receive either of the medications. The administration of either digitalis or methantheline bromide prophylactically prior to operation (groups II and III) reduced the frequency of these reactions. The medical patients studied consisted of patients with hypertension and peripheral vascular disease. These patients were given methantheline bromide, 50 to 150 mg. orally, or 5 to 8 mg. intravenously. Studies of the effect of methantheline bromide on the sympathetic nervous system revealed that the drug did not produce postural hypotension, did not block the normal pressor reaction to blowing, did not abolish the cold pressor reaction, but did inhibit somewhat the vasoconstrictor reflexes induced by digitalis. Studies on patients with increased vagal tone due to digitalis intoxication indicated that methantheline bromide is a powerful antagonist to the vagotonic effects of digitalis. The authors suggest that combinations of digitalis and methantheline bromide preoperatively should make it possible to obtain the advantages of digitalis preoperatively in certain patients without increasing the danger of severe or fatal vagal cardiovascular reactions which have in the past been a contraindication to the preoperative use of digitalis.

SAGALL

Deterling, R. A.: The Use of Dioxyline Phosphate in Peripheral Vascular Disorders. Angiology **4:** 397 (Oct.), 1953.

Dioxyline phosphate is a synthetic papaverine-like compound. The clinical effects of this drug were observed in 127 patients suffering from a variety of peripheral vascular disorders: arterial embolism or thrombosis; arteriosclerosis; thromboangiitis obliterans; arteritis; arteriovenous fistula; glomus tumor; Raynaud's phenomena; "postvisualization" spasm; varicose veins; and phlebitic states. The majority of patients received 200 to 400 mg. by mouth four times daily. In a few instances, 100 mg. doses were injected intraarterially. No toxicity to

the drug has been noted in patients receiving 0.6 to 1.8 Gm. of drug orally for periods of time as long as 18 months. Side effects have been very rare and mild.

Although it was difficult to be certain how much of the clinical improvement was due to dioxyline phosphate or to other concurrent therapeutic measures, the best results were observed in the postphlebitic syndrome. Benefit was also noted in patients with arterial embolism or thrombosis, Raynaud's phenomena, and early thromboangiitis obliterans or arteriosclerosis.

WESSLER

Siebens, A. A., Hoffman, B. F., Enson, Y., Farrell, J. E., and Brooks, C. McC.: Effect of l-Epinephrine and l-Nor-Epinephrine on Cardiac Excitability. Amer. J. Physiol. **175:** 1 (Oct.) 1953.

Both *l*-epinephrine and *l*-norepinephrine first lower then increase the diastolic thresholds to electrical stimulation. The lowered threshold is associated with an increased serum potassium in the case of epinephrine. Hepatectomy abolishes the change in potassium and decreases the epinephrine effect on threshold but has little or no influence on norepinephrine action on the thresholds. Both agents produce tachycardia in vagotomized dogs. Epinephrine has more effect on conduction velocity than norepinephrine. Each produces a similar slight shortening of relative and absolute refractory periods in atrial and ventricular musculature.

OPPENHEIMER

Murphy, E. A., and Eastwood, J.: Hexamethonium in Polyvinylpyrrolidone. Lancet **265:** 804 (Oct. 17), 1953.

In an effort to obviate the need for frequent injections of methonium compounds, the authors investigated the use of a single daily subcutaneous injection of a solution of 20 per cent hexamethonium bromide in Polyvinylpyrrolidone, a plasma substitute, in five patients with severe hypertension. This combination seemed to have an effective hypotensive action which persisted for from 6 to 12 hours, and in some cases throughout the 24 hours. There was a slight tendency to be cumulative. Because of its irregular action, however, with unpredictability in the development of hypotension, it was felt to be more inconvenient that multiple injections of simple aqueous solutions of hexamethonium.

MAXWELL

Evans, B. M., Hughes Jones, N. C., Milne, M. D., and Yellowlees, H.: Ion-Exchange Resins in the Treatment of Anuria. Lancet **265:** 791 (Oct. 17), 1953.

The treatment of five cases of anuria or severe oliguria complicated by hyperkalemia with a sodium sulphonic ion-exchange resin is reported. It was administered both by mouth (15 Gm. three to four times daily) and by retention enema (15 Gm. daily) while the patients were treated with a high caloric electrolyte-free diet or daily intravenous infusions of hypertonic (40 per cent) glucose into the superior vena cava through a polythene tube.

The serum potassium level was satisfactorily reduced in four of the patients, the fifth patient dying from hyperkalemia before the resin could exert any significant effect. Appropriate fecal analyses at necropsy revealed that the potassium uptake continued throughout the gastrointestinal tract. The effect is therefore delayed after the first dose and prolonged after the last one. The resin was more effective when given by mouth than when given by retention enema, in the former instance exchanging 0.5 to 1.2 mEq. of potassium per gram, corresponding to a total of 20 to 75 mEq. a day at the dosage used. It was suggested that resin treatment be started as soon as the serum potassium level rises above 6 mEq. per liter, and be discontinued when it falls below 5 mEq. per liter. A scheme of routine treatment with ion-exchange resins is given for anuria and severe oliguria.

MAXWELL

Boyadjian, N., and Van Dooren, F.: The Action of Procaine Amide on Auricular Arrhythmias. Arch. mal. coeur **46:** 941 (Oct.), 1953.

Procaine amide used parenterally is capable of suppressing all forms of auricular arrhythmias. Experimental auricular fibrillation produced in the dog by acetylcholine could invariably be converted to normal rhythm by intravenous application of nontoxic doses of the drug. In man the results were less consistent. Paroxysmal auricular fibrillation of recent origin is readily reversible, while in chronic forms procaine amide proved practically inactive. In other forms of auricular tachycardias and in auricular premature beats the results were variable. In general, larger doses are necessary than for suppression of ventricular arrhythmias. With doses not exceeding 1000 mg., no inconvenience was caused by intravenous injection of procaine amide. Oral application had, in the experience of the authors, only little effect on auricular arrhythmias. It is concluded that procaine amide cannot replace quinidine in the treatment of disorders of auricular rhythm, but it does constitute a valuable additional therapeutic agent.

PICK

Brown, A. S.: Transfusion by the Intra-arterial Route. Lancet **265:** 745 (Oct. 10), 1953.

After briefly reviewing the history of intra-arterial transfusion, the author presents his clinical impressions based on the use of this technic in 165 cases, largely consisting of neurosurgical patients in whom retrograde intra-arterial injection was used to replace blood withdrawn for preoperative exsanguina-

tion or lost accidentally when large vessels were torn during the removal of vascular tumors. In addition to direct blood pressure measurements from the radial artery in all instances, plethysmographic records were obtained from the lower extremities of 10 consecutive cases in an effort to delineate the hemodynamic alterations which took place.

Retrograde intra-arterial administration of blood consistently proved superior to the intravenous route in combating hypotension and restoring circulatory dynamics. This was especially evident in those patients in whom hypotension had been severe and prolonged. In this latter group, intravenous therapy produced only temporary improvement whereas intra-arterial transfusion, even in small amounts, usually resulted in permanent resuscitation.

Interpretation of the combined blood-pressure recordings and plethysmograms suggest that there is an immediate decrease in peripheral vasoconstriction after the initiation of arterial transfusion. Vascular tone returns to the control level with the termination of the transfusion, followed in a few minutes by a further decrease in vasoconstriction and, in the presence of an unaltered blood pressure an increase in cardiac output. A rise of blood pressure only occurred several minutes after the first change in peripheral blood flow had become apparent.

It is concluded that intra-arterial transfusion is of advantage in the treatment of patients who have become exsanguinated to critical levels, or are in severe circulatory failure for other reasons. Emphasis is placed on the danger of gangrene incident to arterial infusion of plasma, saline or other non-oxygen-bearing fluids.

MAXWELL

Kierland, R. R., Brunsting, L. A., and O'Leary, P. A.: Quinacrine Hydrochloride in the Treatment of Lupus Erythematosus. Proc. Staff Meet., Mayo Clinic **28:** 636 (Nov.), 1953.

During 1952, the authors treated with atabrine 60 patients who had lupus erythematosus. Fifty-five of these patients had the chronic discoid form of the disease, and five had moderate systemic manifestations of lupus erythematosus. Of the 55 patients with chronic discoid lupus erythematosus, 52 have been followed either directly or by correspondence. The results obtained are as follows: 11 patients were 0 to 25 per cent improved (one of these reported that he became worse); 9 were 25 to 75 per cent improved; 15 were more than 75 per cent improved but the disease was not arrested; and 17 had complete arrest of the disease. Twenty-one of the patients had stopped taking atabrine. Subsequently, 10 of these had had recurrences while 11 had not, in observation periods extending to more than six months. Several of the patients who had been receiving low maintenance doses of 50 to 100 mg. of atabrine daily noted that after exposure to the sun during the spring, some of the lesions of lupus erythematosus again became active after several months of inactivity.

It is necessary to remember the potential serious sequelae of therapy with atabrine. Reactions are similar to those of gold, arsenic, and, to a lesser degree, bismuth. The incidence of reactions from atabrine is less frequent than from the heavy metals. The skin participates with the greatest frequency in these undesirable reactions by an eruption which simulates one of the following: lichen planus, pityriasis rosea, seborrheic dermatitis or dishidrosis. The incubation period of the lichenoid reaction is long. In a series of patients studied previously, it varied from six weeks to nine months, the greatest number of reactions appeared three to six months after treatment with atabrine was begun. Untoward reactions may involve the hematopoietic system, in the form of an aplastic anemia, the central nervous system, the gastrointestinal system or the liver.

SIMON

Assali, N. F., Kaplan, S., Oighenstein, S., and Suyemoto, R.: Hemodynamic Effects of l-Hydrazinophthalazine (Apresoline) in Human Pregnancy: Results of Intravenous Administration. J. Clin. Investigation **32:** 922 (Oct.), 1953.

The explanation of the mechanism of the action of hydrazinophthalazine is not entirely clear. It is effective in reducing the hypertension of pregnancy toxemia and in acute nephritis. In this investigation the hemodynamic effects of intravenous injection of this substance were studied in 12 nonpregnant, normotensive, healthy women, 12 pregnant but normotensive women, 33 women with toxemia of pregnancy, and 18 women who were pregnant and had essential hypertension. Hydrazinophthalazine was given by rapid single intravenous injection in doses ranging from 20 to 40 mg. Some of the findings in this study were as follows: in the normotensive patient there was a slight fall in blood pressure, but in the toxemic group there was a significant and prolonged hypotensive response. A moderate blood pressure fall was noted in the patients with essential hypertension.

Furthermore, there was a significant increase in cardiac output and a reduction in the peripheral resistance at the height of the hypotensive effect, with no change in blood volume.

The temperature in the upper extremities rose considerably in contrast to the slight change in the lower extremities. These findings differ from those following ganglionic blockade in which the reverse effect is produced, and point to differences in mechanisms controlling blood flow to various segments of the body. The drug did not block the vasopressor response to cold, or the Valsalva maneuver in the pregnant women.

WAIFE

Malinow, M. R., Batlle, F. F., and Malamud, B.: Nervous Mechanisms in Ventricular Arrhythmias Induced by Calcium Chloride in Rats. Circulation Research **1:** 554 (Nov.), 1953.

Ventricular flutter and fibrillation induced by standardized doses of calcium chloride in rats were prevented by sympatholytic and autonomic blocking drugs (tetraethylammonium chloride, hexamethonium bromide, Hydergine), by encephalic and/or upper spinal destruction and by medullospinal section. Bilateral vagotomy, bilateral adrenalectomy, and lower spinal cord destruction did not prevent these arrhythmias.

These results suggest the neurogenic origin of induced arrhythmias, with probable centers within the brain stem; impulse conduction occurs through the upper spinal cord and then to the heart via sympathetic pathways. Direct arrhythmic effects of higher concentrations of calcium chloride upon the myocardium were also noted. The pathogenic and pharmacologic similarities with other ectopic rhythms, experimentally produced in different species or spontaneously arising in man, were discussed.

MAXWELL

Malinow, M. R., Batlle, F. F., and Malamud, B.: Prevention of Neurogenic Ventricular Arrhythmias in the Rat by Autonomic Blocking Drugs. Am. J. Physiol. **175:** 8 (Oct.) 1953.

Calcium chloride produces ventricular flutter and fibrillation in rats. This may be prevented by tetraethylammonium chloride (TEAC) or hexamethonium bromide. Protection does not depend on hypotension since a low blood pressure due to hemorrhage does not protect. These blocking agents still protected although pressure was elevated by transfusions. The authors are of the opinion that calcium chloride induces ventricular flutter and fibrillation by neurogenic mechanisms. These pathways may be blocked by the two agents studied.

OPPENHEIMER

PHYSICAL SIGNS

Kerr, A. Jr., and Palmer, E. D.: The Balthazar-Foster Murmur and Foster's Rule. New England J. Med. **248:** 1064 (June 18), 1953.

In 1866 and 1867, Foster described a loud murmur of aortic regurgitation, a mitral systolic murmur well transmitted to the axilla and a peculiar prolongation of the second sound, "sometimes almost a murmur" in a patient with rupture of the "left semi-lunar segment of the aortic valve." Later he reported two cases of aortic-valvular cusp rupture in which there was a diastolic murmur of aortic insufficiency well transmitted to the ensiform cartilage but not to the heart's apex; in each case the cusp which ruptured had a coronary artery arising from its adjacent sinus of Valsalva. In 1874, Foster stated his rule that "incompetency of the left leaflet is associated with transmission of the diastolic murmur to the apex and that insufficiency of either the posterior or right leaflets results in transmission of the murmur to the ensiform." In another publication, Foster changed his nomenclature of the aortic valves referring to the noncoronary leaflet as a posterior segment and changed his rule accordingly. In 14 cases reported by these observers, the following was observed: (1) when the noncoronary cusp was involved, the transmission of the murmur was to the apex in four cases, to the ensiform in three cases and to both areas in two cases; (2) when the left coronary-artery segment was involved, the transmission was to the apex in two cases and to the ensiform in three cases. An Austin-Flint murmur was present with involvement of a noncoronary cusp in three cases, and in association with a coronary cusp in two cases.

The Foster murmur is considered ambiguously described and has been variously interpreted. It is felt that the Foster rule has not been confirmed by previous reports nor by an analysis of further cases. It is felt, further, that the prediction of which cusp of the aortic valve is incompetent, either from the transmission of the aortic diastolic murmur or on the basis of an Austin-Flint murmur, is hazardous.

ROSENBAUM

Silverman, J. J., and Littman, D. S.: The Cardiologist Looks at the Hand. New England J. Med. **249:** 839 (Nov. 19), 1953.

The authors point out the importance of simple but careful examination of the hand, and discuss a number of conditions in which examination of the hand yields important clinical information regarding the cardiovascular system of the patient. The size of the fist may give a rough estimate of the size of the heart, since under normal conditions a small fist usually indicates a small heart. Anxiety states, such as neurocirculatory asthenia, may be indicated by cold, flabby, wet hands; increased palmar sweating; tremor; restless and fidgety hands; cyanosis and mottling; or tobacco stained fingers. In congenital heart disease clubbing of the fingers is generally proportional to the degree of cyanosis and appears only after cyanosis has developed. Congenital anomalies such as syndactyly, polydactyly, and arachnodactyly may be associated with congenital heart disease. Small, slowly growing para-ungual fibromas have been reported in tuberous sclerosis of the brain, a condition in which rhabdomyoma of the heart has been described. In mongolism the incidence of congenital heart disease is almost 25 per cent. The hand in mongolism is often distinctive, being fat and flabby with short cone-shaped fingers and a rudimentary second phalanx of the little finger. In subacute bacterial endocarditis a number of important clinical findings often can be detected in the examination of the hand, e.g., Osler's nodes the Janeway lesion, trophic disturbances, petechial

hemorrhages, "splinter hemorrhages," embolic phenomena, clubbing of the fingers, and pallor. Clues to endocrine disturbances which may be associated with or complicate cardiovascular disorder may often be found in the hand—the warm, moist hand of hyperthyroidism; the rough, dry, cold hand of myxedema; the broad pale, large hand of acromegaly; the underdeveloped hand of cretinism; etc. Myocardial infarction may be complicated by the shoulder-hand syndrome with resultant changes in the hand. In metabolic diseases such as xanthomatosis, or gout, the lesions may be confined to the hand. Disturbances of liver function may be suggested by the findings of erythema of the palms or spider angiomas. Deficiency conditions developing in patients with long standing cardiovascular disorders may be recognized at times by changes in the hands. Raynaud's syndrome and erythromelalgia involving the hands and fingers may be secondary manifestations of a variety of conditions. In the diffuse collagen diseases the hands are frequently involved. The hands disclose evidences of changes of the peripheral circulation. Changes in the color and temperature of the skin of the hands may be the first indication of impending peripheral vascular collapse. Thus, simple observation and palpation of the hand is of great value in cardiovascular problems.

SAGALL

PHYSIOLOGY

Twarog, B. M., and Page, I. H.: Serotonin Content of Some Mammalian Tissues and Urine and a Method for Its Determination. Am. J. Physiol. **175:** 157 (Oct.), 1953.

The isolated heart of the mollusc, Venus mercenaria, was used to evaluate serotonin activity. Serotonin was detected in brain (dog, rat, rabbit) and in dog and human urine. Intravenous injection of serotonin increases urinary excretion. Serotinin activity was not detected in citrated blood from heparinized dogs although there were detectable amounts in the serum. These latter facts were unchanged by infusion of large quantities of serotonin.

OPPENHEIMER

Frank, H., and Gray, S. J.: The Determination of Plasma Volume in Man with Radioactive Chromic Chloride. J. Clin. Investigation **32:** 991 (Oct.), 1953.

Radioactive chromic chloride is rapidly bound by plasma proteins, to the extent that 98 per cent or more is bound immediately upon intravenous injection. Apparently the chromic chloride can leave the circulation only at the rate at which proteins leave it; hence it would appear to be useful for the determination of the plasma volume.

Determinations in 21 normal adult males, using the isotope dilution principle, gave results which are said to be accurate to within 3 per cent as verified by hemorrhage and transfusion experiments with measured volumes of plasma. The mean circulating plasma volume in the adult male group studied was 2,894 ml. ± 366. The mean plasma volume per kilogram was 39.3 ml. ± 4.9; and the mean plasma volume per square meter of body surface area was found to be 1515 ml. ± 157.

The half-life of radioactive chromic chloride is 26.5 days. There did not seem to be significant accumulation of Cr^{51} in the spleen, however, the accumulation may be greater in patients with rapid hemolysis.

WAIFE

Gray, S. J., and Frank, H.: The Simultaneous Determination of Red Cell Mass and Plasma Volume in Man with Radio-Active Sodium Chromate and Chromic Chloride. J. Clin. Investigation **32:** 1000 (Oct.), 1953.

Because of the selective affinity of red cells for hexavalent anionic chromium^{51}, and of the plasma proteins for trivalent cationic Cr^{51}, both forms of the isotope were used for the simultaneous determination of red cell mass and plasma volumes by the isotope dilution principle. It was found that the mean values for red cell mass and plasma volume obtained by the combined method agreed favorably with those obtained when chromic chloride and sodium chromate were used separately. This is because the affinity of chromic chloride for the plasma proteins is such that less than 2 per cent of the injected material is lost to the red cells while the bond of sodium chromate to erythrocytes is sufficiently strong so that there is no significant loss of radioactivity to the plasma.

WAIFE

RHEUMATIC FEVER

Ansell, B. M., Antonini, F., and Glynn, L. E.: Cantharides Blisters in Children with Rheumatic Fever. Clin. Sc. **12:** 367 (Nov.), 1953.

The authors used a standardized procedure for raising cantharides blisters in the skin of the abdominal wall, removing the blister fluid, and studying its volume, cytology, and protein content. The method was found to be painless and trouble free. Thirty children with rheumatic fever, five children with other illnesses, and six normal children were studied.

The volume of blister fluid was found to be consistently lower in the acute rheumatic fever patients than in the others. With treatment of rheumatic fever, the only significant change occurred in the patients receiving corticotropin. These patients, despite suppression of clinical activity, showed still further diminution in volume of blister fluid. White cell counts did not vary substantially in any of the groups, and eosinophil counts were too variable to have statistical correlation. The protein content of blister fluid was generally related to that of the

subjects plasma, and the ratios of blister-plasma albumin were the same in all groups. However blister-plasma globulin ratios were higher in acute rheumatic fever, and fell during treatment.

The appearance of the blisters differed in that those in acute rheumatic fever were covered by thick, edematous skin; those of normal or convalescent subjects had a covering about one-fifth as thick; and those of corticotropin treated cases had an extremely thin covering. These differences in appearance of the blisters and their blister-plasma globulin ratios between cases of untreated rheumatic fever and corticotropin cases suggest that the mechanisms differ. In the latter cases, it is probable that less fluid is exuding from capillaries. In the untreated cases, the effect of cantharides on capillary permeability is probably as great as in normal persons, but the fluid may be excessively diffused through the tissues instead of remaining localized in the blister. This may be adduced as additional evidence of a generalized involvement of connective tissue in acute rheumatic fever.

ENSELBERG

Jackson, R. L., Kelly, H. G., Smith, E. K., Wang, P., and Routh, J. I.: Electrophoretic Analyses of Plasma or Serum Proteins of Rheumatic-Fever Patients in Relation to Stages of Disease. J. Dis. Child. **86:** 403 (Oct.), 1953.

Electrophoretic patterns of the proteins of 205 plasma or serum samples from 77 children with definite rheumatic fever and five patients with chorea alone were analyzed in relation to the course of the disease.

In the acute state, the percentage composition of albumin is significantly decreased, whereas fibrinogen and the globulins ($alpha_1$, $alpha_2$, gamma′ and gamma) are increased. The return to normal values as the disease regresses is gradual for albumin, fibrinogen, $alpha_2$ and gamma globulins; $alpha_1$ and gamma′ globulins are elevated generally only in the acute stage. The beta globulin component seems to be unaltered by the disease. The mean values for total proteins are slightly elevated for all subgroups of uncomplicated rheumatic fever and significantly elevated in the late-subacute stage. Serum protein fractions for the group of inactive rheumatic patients indicate that the rheumatic fever patients as a group are capable of normal protein metabolism. The patterns of alteration are discussed in relation to some of the known acute-phase reactions, tests and antibody production.

MAXWELL

El-Mazny, A., and Alfy, O.: The Q-T Interval in Rheumatic Fever. Arch. Pediat. **70:** 333 (Oct.), 1953.

The Q-T interval was measured in 30 electrocardiograms of children during the active stage of rheumatic carditis. Ten normal children were studied as controls. All the measurements were taken from lead II, employing a Siemens' string electrocardiographic machine. Taking Goldberger's figure of 1.08 as the upper limit of normal, one-third of the children with active rheumatic carditis showed a prolonged Q-T interval; none of the controls showed such prolongation. It appeared that a prolonged Q-T interval may be found during the active stage of the disease, but a normal measurement does not invalidate the diagnosis of active carditis.

MAXWELL

Taquini, A. C., Lozada, B. B., Donaldson, R. J., D'Aiutolo, E. H., and Ballina, E. S.: Mitral Stenosis and Cor Pulmonale. Am. Heart J. **46:** 639 (Nov.), 1953.

The authors have studied a group of patients with mitral stenosis who have the following signs and symptoms: (1) a history of pronounced respiratory symptoms; (2) an extreme degree of dyspnea; (3) electrocardiographic and roentgenographic evidence of marked right ventricular hypertrophy; (4) the early appearance of congestive heart failure; and (5) marked alterations in circulatory dynamics with extremely high pressures in the pulmonary circulation. The name of "mitral stenosis and cor pulmonale" has been given to this group. The importance of identifying this type of case lies in the present ability to operate upon the stenosed mitral valve. The pulmonary changes which characterize these cases may be reversible when arrested at the initial stages of their development but are most probably unchangeable when far advanced.

RINZLER

Williams, M. H., Jr.: Pulmonary Function Studies in Mitral Stenosis before and after Commissurotomy. J. Clin. Investigation, **32:** 1094 (Nov.), 1953.

In a group of nine cases of mitral stenosis studied before and after commissurotomy, it was found that several showed an increase in the effective shunting of blood through the poorly aerated lung, in some instances with arterial unsaturation. This abnormality was largely corrected by commissurotomy. Prolonged rest in the supine position increases pulmonary congestion. Resting hyperventilation frequently disappeared after operation, suggesting that the engorged pulmonary bed serves as a reflex stimulus to ventilation.

WAIFE

Schlegel, B., and Schoelmerich, B.: Roentgenkymographic and Phonocardiographic Studies of the Hemodynamics of the Left Atrium in Mitral Stenosis. Ztschr. Kreislaufforsch. **42:** 848 (Nov.), 1953.

Kymographic and phonocardiographic findings in mitral disease and their postural variations are reported. According to the authors, a marked proto-

diastolic movement in ventral direction of the left atrial border (in the right anterior oblique diameter) suggests that a stenosis of the mitral ostium is not of significant degree. The slighter the stenosis, the more pronounced is the protodiastolic portion of the left atrial kymogram which may even assume a plateau like contour. The finding of a dorsal movement of the atrial border in the protodiastolic phase suggests the presence of mitral insufficiency. All these alterations become more pronounced with the patient in supine, head low, position. Registration of the apical phonocardiogram in various positions permits an estimation of the degree of mitral stenosis by comparing the intensity of diastolic and presystolic murmurs in erect and in lying positions. The authors believe, that the combined use of these two methods represents "an advance in the assessment of inflow and outflow to and from the left atrium."

PICK

ROENTGENOLOGY

Comstock, S. W.: Mortality of Persons with Photofluorograms Suggestive of Cardiovascular Disease. New England J. Med. **248:** 1045 (June 18), 1953.

This report is concerned with results of the photofluorographic survey of 43,429 persons in Muscogee County, Georgia. Of these, 739 or 1.70 per cent, had chest photofluorograms considered indicative of cardiovascular abnormalities. Abnormalities were more frequent in males and in negroes and increased markedly with advancing age. Hypertensive and cardiovascular syphilitic disease was more common in negroes. Of the 739 cases discovered in this survey, 116 (15.7 per cent) were known to have died in the three and one-half year period following the survey. The mortality increased from 6 per cent for the group from 15 to 34 years of age to nearly 20 per cent for the persons over 55 years of age. In the survey population considered negative for cardiovascular disease, the mortality was 1.15 per cent in whites and 2.09 per cent in negroes. The selected group, less than 2 per cent of the surveyed population, yielded nearly a fourth of the renocardiovascular deaths which occurred among this population in the three and one-half years after the survey. It is felt that a survey such as this can identify among the total surveyed population a relatively small group of persons whose subsequent mortality experience shows that they are in need of further remedial or preventive measures. It is felt that the yield of significant cardiac disease can be considerably increased if the survey films are reviewed by physicians with specialized training.

ROSENBAUM

Dotter, C. T., Lukas, D. S., and Steinberg, I.: Tricuspid Insufficiency. Observations Based on Angiocardiography and Cardiac Catheterization in Twelve Patients. Am. J. Roentgenol. **70:** 786 (Nov.), 1953.

On angiocardiography the authors noted marked right atrial enlargement, dilatation of the superior vena cava, and occasionally irregularities in right atrial filling near the tricuspid orifice where non-opacified blood from the regurgitant jet could be suspected. Right atrial pressure curves indicated systolic filling causing a plateau like wave, with peak pressures up to 31 mm. Hg.

SCHWEDEL

Amundsen, P.: Planigraphy in Muller and Valsalva Experiments. Acta Radiol. **40:** 387 (Oct.), 1953.

Planigrams taken at specified depths indicate alterations in width of venous and arterial channels during inspiration at pressures of minus 30 to 60 cm. of water, and expiration at pressures of 40 to 60 cm. The vena azygos, superior vena cava, and the veins and arteries to and from an arteriovenous aneurysm (hemangioma) show alterations in size, increasing during inspiration, diminishing in expiration. Nonvascular tumors and glands, on the other hand, show no such change in size.

SCHWEDEL

SURGERY IN HEART AND VASCULAR SYSTEM

Björk, V. O., and Crafoord, C.: The Surgical Closure of Interauricular Septal Defects. J. Thoracic Surg. **26:** 300 (Sept.), 1953.

The authors review the various technics for closure of interauricular septal defects and present a new approach to the problem. The blind methods consist of either compressing the anterior wall to the posterior wall of the auricles by means of sutures through the heart, invaginating auricular appendages into the septal defect, or using a clamp to approximate the auricular walls against the septum. One of the closed intracardiac tactile methods involves the attachment of the lateral right auricular wall to the septum at the periphery of the defect, and using a finger, inserted through the auricular appendage, to guide the placement of sutures. Another utilizes a cone-shaped rubber bag attached to the wall of the auricle so that this chamber can be opened and blood allowed to rise up into the rubber well.

The new method described by the authors consists of dissection between the superior vena cava and pulmonary vein until a considerable groove is produced. Then a finger is inserted into the right auricle through its appendage and a needle is guided subendocardially in the septal plane. The needle follows the aorta down and through the upper portion of the interventricular septum and comes out through the left auricular wall behind the inferior vena cava, close to the annulus fibrosus. The two ends of the silk suture thus drawn through are tied in the dissected groove between the superior vena cava and the pulmonary veins. The method appears to be applicable even in the case of a very large

interauricular septal defect without a septal rim. It has been utilized successfully in one patient.

ABRAMSON

Keefer, E. B. C., and Moore, S. W.: The Clinical Use of Homologous Arterial Grafts. Bull. New York Acad. Med. **29:** 701 (Sept.), 1953.

Homologous vascular grafts preserved in a blood vessel bank are of value in the surgical treatment of a number of conditions. The criteria for their implantation may be present in the following cardiovascular lesions: infantile type of coarctation of the aorta in an adult patient, adult type of coarctation of the aorta, congenital lesions requiring shunting procedures, aneurysms, trauma to a major vessel, segmental obliterative arterial disease, cancer or tumor invasion of a major blood vessel, and a smaller number of unusual conditions. The results of 12 cases in which arterial grafts were employed are tabulated. Two cases in whom the need of an arterial graft was not predicted pre-operatively but in whom their use made a hopeless situation operable are reported.

SAGALL

Sealy, W. C.: Indications for Surgical Treatment of Coarctation of the Aorta. Surg., Gynec. & Obst. **97:** 301 (Sept.), 1953.

The author presented the results obtained with surgical treatment of 22 patients with coarctation of the aorta. Of this number, death occurred in two. In one of these, the junction of the aortic arch and subclavian artery was found to be necrotic, while in the other death was due to numerous infarcts in vital organs. In 19 of the successful cases, the systolic pressure, which was previously elevated in the upper extremities, returned to normal postoperatively.

It was the opinion of the author that when coarctation of the aorta is associated with another cardiac anomaly or disease, the additive effect of the two may be such that failure of the circulation is likely to occur. Therefore, under such circumstances, surgical intervention is indicated. This approach is also advisable in order to prevent the occurrence of accidents or infection in the region of the coarctation. The influence of age likewise plays a role in determining the type of therapeutic program to adopt. In the very young the operation is mandatory if adequate circulation cannot be maintained and development is retarded. When the patient is 5 to 10 years of age, the technical advantages of performing the operation at this time outweighs the advantages of waiting longer to permit further growth at the anastomotic site. In individuals above the age of 30 years, the operation becomes most hazardous and hence its indications must be clear-cut and unequivocal.

ABRAMSON

Duff, R. S.: Effect of Surgical Sympathectomy on the Sensitivity to Epinephrine of the Blood Vessels of Muscular Segments of the Limbs. J. Clin. Invest. **32:** 851 (Sept.), 1953.

When blood vessels are deprived of their sympathetic nerve supply, there is an increased sensitivity to epinephrine. There seem to be two phases to this reaction. During intravenous epinephrine infusion, marked vasodilatation of the forearm occurred early, both in normal and sympathectomized limbs. Following this, there is a second phase of moderate dilatation in normal, but not in sympathectomized limbs. Because of its absence in chronically sympathectomized areas, this secondary vasodilatation was thought to be an indirect effect mediated by the sympathetic nerves. In this study it was found that the initial vasodilatation in the forearm and calf during the intravenous infusion of 10 μg. of epinephrine per minute was greater in the sympathectomized than in the normally innervated limbs. The observations reported here suggest that the sustained moderate vasodilatation in normally innervated forearms and calves during the second phase was due to some nonlocal effect of epinephrine. This is believed to be due to hypersensitivity of the vessels.

WAIFE

Glenn, F., and Stewart, A. J.: Mitral Commissurotomy. Bull. New York Acad. Med. **29:** 677 (Sept.), 1953.

Mitral commissurotomy is indicated for patients who have mitral stenosis predominately and only a minimal degree of mitral insufficiency, and who are experiencing progressive disability. Auricular fibrillation, cardiac enlargement, minimal aortic lesions, age, and congestive heart failure are not contraindications. Presently accepted contraindications consist of bacterial endocarditis, active rheumatic fever, severe mitral regurgitation, or severe involvement of other valves. The anesthesia should be light and combined with a high oxygen intake. The authors approach the heart through resection of the left fourth rib. Valvuloplasty in most cases can be performed by finger fracture. In a few cases a valvulotomy is necessary. The object is to create a valve area of from 4 to 6 cm. in diameter with minimal regurgitation. Over the past eight months 33 patients have been operated upon at the New York Hospital-Cornell Medical Center. Two deaths occurred with the first eight patients and none with the last 25. Eighteen of the first 20 operated patients are alive, and 11 are markedly improved. Three have shown slight improvement and four no improvement. The remaining 13 patients were operated upon in the past six months, and although it is too early to make any conclusion the results appear more promising than in the original 20.

SAGALL

De Bakey, M. E., and Cooley, D. A.: Surgical Treatment of Aneurysm of Abdominal Aorta by Resection and Restoration of Continuity with Homograft. Surg., Gynec. & Obst. **97**: 257 (Sept.), 1953.

Seven cases of abdominal aneurysm were treated by resection of the involved portion and restoration of continuity of the vessel using aortic homografts. In each instance the lesion was located below the origin of the renal arteries. In all but one it was of arteriosclerotic origin. Aortography was employed as a diagnostic procedure in five patients. There was one death in the series, this occurring on the thirteenth day postoperatively as a result of progressive uremia and secondary hemorrhage. The remaining patients demonstrated excellent results.

It was concluded that resection of the aneurysm and involved segment of aorta, with restoration of normal flow by means of an aortic homograft, was the procedure of choice in the treatment of this condition.

ABRAMSON

Artusio, J. F., Jr.: Anesthesia Management of the Rheumatic Cardiac for Mitral Valvulotomy. Bull. New York Acad. Med. **29**: 684 (Sept.), 1953.

Prior to operation the patient should be in the best possible physical condition. In the author's cases morphine and atropine were given subcutaneously one and one-half hour prior to induction of anesthesia. The anesthetic technic has been a closed circle carbon dioxide absorption endotracheal method with an inflated cuff to maintain a completely closed system. Pentothal sodium (2½ per cent) was the anesthetic agent used initially. Anesthesia was then induced with ether-oxygen, using 50 per cent oxygen and 50 per cent nitrous oxide to accomplish the Pentothal-ether sequence. Intubation was performed in the first plane of the third stage of anesthesia using a local spray of topical 2 per cent xylocaine. When the chest is opened assisted respiration is employed cautiously, but controlled respiration should not be utilized. The operating cardioscope was of great value in following cardiac rate and rhythm. The greatest number of irregularities occurred during manipulation of the heart valve and are related to movement of the finger. Blood should be given only as necessary to replace the amount lost, for circulatory overload occurs easily in these patients. Blocking the upper thoracic nerves in the paravertebral region with 2 cc. of Efocaine greatly reduces the incidence of severe postoperative pain in this region.

SAGALL

Mears, E. J., Harvey, W. P., and Hufnagel, C. A.: Relief of Pulmonary Hypertensive Pain After Mitral Commissurotomy. New England J. Med. **249**: 715 (Oct. 29), 1953.

The authors present in detail the case of a mitral commissurotomy performed on a 50 year old woman with mitral stenosis and insufficiency, pulmonary insufficiency, auricular fibrillation and cardiac decompensation. During the 25 years prior to operation she had frequent, severe substernal and precordial pain, precipitated by exercise and relieved by nitroglycerine. These attacks soon became refractory to nitroglycerine and frequent administration of narcotics was required for relief and for 15 years the patient had been incapacitated by daily attacks of pain. At operation a tight mitral valve was successfully opened. Postoperatively there was immediate relief from the precordial pain. During a 10-month follow-up period the patient has been entirely free of pain except when cardiac decompensation becomes manifest. With control of decompensation by diuretics the pain disappears. This patient substantiates the validity of pulmonary hypertensive pain as an entity which can simulate the pain of angina pectoris and coronary artery disease and affords evidence that the pain is related to increased pressure in the pulmonary circuit.

SAGALL

Moore, H. G., Jr., Nyhus, L. M., Kanar, E. A., and Harkins, H. N.: Preliminary Experimental Observations on the Nature, Extent and Repair of Gunshot Injuries of the Aorta. West. J. Surg. **61**: 607 (Oct.), 1953.

The authors studied the effect of experimentally produced gunshot wounds of the abdominal and thoracic aorta of dogs. It was found that when normotensive aortas that were exposed to air were shot with .177 caliber missiles, the defects were much larger than in the case of hypotensive vessels. Covering the normotensive aorta with a shallow layer of saline solution before it was traumatized produced much smaller defects.

It was concluded that the destruction of an artery by a gunshot was due to two factors: (1) the hole made by the simple passage of the missile through the wall; and (2) the "bursting" component due to displacement and overstretching of the arterial wall by the pressure changes adjacent to the missile, and the temporary cavity which followed. It was also found that the gross intimal damage usually exceeded the gross external damage. Because of such changes, it was suggested that the optimal method of debridement and repair was the use of segmental resection of the injured vessel at least 3 mm. beyond the gross defect, followed by axial anastomosis.

ABRAMSON

Fraser, R. S., and Chapman, C. B.: The Cardiovascular Effects of Cervicothoracic Vagectomy in

the Human Being. New England J. Med. **249:** 837 (Nov. 19), 1953.

The authors report the results of cardiovascular studies in a 40 year old farmer four months after a bilateral vagectomy had been performed for removal of neurofibromata of both vagi. The vagectomy was complete on the left side and nearly complete on the right and probably resulted in the severance of most of the vagal efferent pathways to the heart. The cardiac output increased from the resting level of 5.33 liters per minute to 10.21 liters per minute after exercise, and the circulation time decreased from 19.7 seconds to 14.6 seconds. These values were within normal limits. Blood pressure changes during exercise likewise were the same as in normal subjects. The pulse rate remained persistently high after operation and was not changed after a subcutaneous injection of atropine. In response to exercise the pulse increased somewhat less than normal. These observations suggest that marked reduction in vagal influence on the heart by parasympathetic denervation in the human being results in a permanent increase in the resting heart rate but does not alter the normal circulatory adjustments to moderately heavy exercise. Thus, in the human, these adjustments are probably carried on by important nonvagal mechanisms.

SAGALL

Peirce, E. C., II, and Polley, V. B.: Differential Hypothermia for Intracardiac Surgery (Preliminary Report of a Pump-Oxygenator Incorporating a Heat Exchanger). Arch. Surg. **67:** 521 (Oct.), 1953.

A sound technic for intracardiac surgery requires direct-vision access to the entire interior of the heart for prolonged periods plus adequate protection for the brain and other vital organs during cardiac isolation or failure. This cannot easily be provided at normal temperatures because of the technical difficulties presently inherent in large capacity extracorporeal pump-oxygenators. The protective action of reduced metabolism provided by hypothermia is but a partial solution to the problem. Combined with a low capacity pump-oxygenator, however, hypothermia provides safety during lengthy cardiac isolation or failure. Direct cooling or warming of the blood is much simpler than external heat exchange, and in addition provides a saving in time and total caloric transfer, the heart and presumably other vital organs being cooled much more rapidly than the animal as a whole.

Experiments in large dogs using a low capacity pump-oxygenator incorporating a heat exchanger are described. With flows of about 500 cc. per minute, the heart was cooled to 20 C. in an average of 21 minutes. Caloric exchange was only 34 per cent of that calculated to cool the entire dog. Ventricular fibrillation was well tolerated and reversible. Warming was practicable to 32 C. by direct heating of the blood.

The authors point out that this is a preliminary animal study on dogs and that the details of temperature, blood flow, and oxygenation, in brain, kidney, liver and other vital organs remain to be studied before this method can be considered suitable for use in humans.

DENNISON

Swan, H., et al: Surgery by Direct Vision in the Open Heart During Hypothermia. J.A.M.A. **153:** 1081 (Nov. 21), 1953.

Fifteen patients have undergone cardiac operations while they were in a state of hypothermia with body temperatures ranging from 21.5 to 26 C. In 13 of these patients, circulation was stopped for periods varying from two to eight and one-half minutes, and the operation was performed in the open heart under direct vision. There was only one operative death in this group. All the others did well, except one, upon whom no therapeutic procedure could be performed. Hypothermia was induced during anesthesia by immersing the patient in a tub full of ice water; conversely, warming the patient was achieved in a tube filled with warm water. Prevention of shivering and hyperventilation were important aspects of the cooling technique and potassium appeared to be a valuable agent for combating ventricular fibrillation in the cold patient. Coronary artery air embolism was prevented by a combination of maneuvers of which one of the most important was complete immersion of the heart in salt solution at the time of closure of the cardiotomy. It is felt that direct vision intracardiac surgery could be further explored and expanded in scope since cessation of circulation in the presence of hypothermia allows an essentially bloodless field with reasonable safety for periods up to at least 8 minutes. It is surprising how much can be deliberately accomplished in this period of time.

KITCHELL

Evans, J. A., and Poppen, J. L.: Resection of Anginal Pathway for Relief of Angina Pain. New England J. Med. **249:** 791 (Nov. 12), 1953.

The afferent pathway for anginal pain is composed of sympathetic fibers passing through the inferior cervical ganglion (which is usually fused with the first thoracic ganglion to form the stellate ganglion), and direct fibers from the cardiac plexus which pass through the first, second, third and fourth thoracic ganglions. From there the impulses are conducted through the white ramus to the spinal cord. Fourteen patients with angina pectoris and hypertension were treated with combined thoracolumbar sympathectomy including removal of all or part of the anginal pathway. In two patients without hypertension the anginal pathway alone was resected. The follow-up for the total series of cases was six months to three

years. Complete relief of angina with the exception of a residual sensation of constriction in the throat was obtained in nine patients. Partial but satisfactory relief of pain occurred in four patients. The best results were obtained in those patients in whom bilateral complete resection of the anginal pathway was performed. An increased postoperative exercise tolerance level was found in a number of patients. This suggests the possibility that coronary artery dilatation occurs after sympathectomy and that excessive anginal pain such as angina decubitus or angina of emotion, may be caused by reflex sympathetic dystrophy. Horner's syndrome, postural hypertension, severe sweating in the groins and swollen nasal mucous membranes are possible complications of sympathectomy. The authors recommend that this operation be limited to hypertensive patients with severe angina and to normotensive patients without a recent coronary infarction who have an "over-alarm" anginal syndrome (excessive anginal pain far out of proportion to any necessity of protecting the heart from overexertion).

SAGALL

Kanar, E. A., Nyhus, L. M., Schmitz, E. J., Sauvage, L. R., Moore, H. G. Jr., and Harkins, H. N.: Experimental Vascular Grafts. II. Some Undesirable Gross and Microscopic Changes Observed in Arterial Homografts after Implantation into the Thoracic Aorta of Growing Pigs: a Preliminary Report. American Surgeon **19:** 915 (Oct.), 1953.

Arterial homografts of various lengths and preserved for different periods of time prior to implantation, were grafted into the thoracic aortas of nine weanling pigs. The grafted segments and aortas were examined 35 to 225 days after the operative procedure. All nine homografts were patent and apparently served as satisfactory conduits of blood. No abnormal or newly formed collateral vessels were detected in the region of any graft at the time of its removal. There was moderate fibrosis around each graft and eight of the grafts showed various degrees of calcific degeneration which was sharply limited to the graft and did not involve the host aorta. Early deposition of the calcium material apparently occurred upon the persisting densely grouped elastic fibers of the homografts. The authors suggest that the degenerative changes observed in aortic homografts may be more directly related to the nature of the antibody-antigen responses of the host than to such factors as graft length, or duration or method of graft preservation.

WESSLER

Grady, E. D., and Colvin, E. M.: Treatment of Venous Insufficiency of the Lower Extremities with a Note on the Use of Ascending Phlebography. Am. Surgeon **19:** 936 (Oct.), 1953.

The authors describe a comprehensive program for the treatment of the various types of venous insufficiency that occur in the lower extremities. The indications for the use of sclerosing solutions, vein ligation, vein stripping and lumbar sympathectomy are described. Ascending erect phlebography with 35 per cent diodrast injected into a foot vein is of help in evaluating problem cases.

WESSLER

Larzelere, H. B., and Bailey, C. P.: Aortic Commissurotomy. J. Thoracic Surg. **26:** 31 (July), 1953.

The authors discussed the problem of aortic stenosis and a surgical approach for its treatment. They pointed out that the highly calcified valve was, for the most part, not amenable to corrective surgery, while in the case of minimal or no calcification, commissurotomy was able to part the fused commissures and allow the valve cusps to function as a hinge again. The authors described an instrument which they considered satisfactory in producing separation of the commissures. This consisted of an apparatus with three parallel dilating or separating bars on a swivel mechanism, which could automatically adjust to the remnants of the fused commissures.

A beaded guidewire was first inserted through an incision in the left ventricle made in the center of a purse-string suture. The incision was then enlarged to permit the triradiate dilator head of the instrument to pass along the guidewire into the venticle and upward into the orifice of the aortic valve. After being properly engaged, the blades of the head were extended, pushed forward and pulled back to produce the commissurotomy. After this step the instrument was withdrawn from the heart.

The authors presented the results of commissurotomy in 42 cases of aortic stenosis, with and without other valvular disease. There were seven deaths, a mortality of 16.6 per cent.

ABRAMSON

Anderson, S., and McKissock, W.: Controlled Hypotension with Arfonad in Neurosurgery, with Special Reference to Vascular Lesions. Lancet **265:** 754 (Oct. 10), 1953.

The results are reported of a trial of the vasodepressor agent, Arfonad [*d*-3,4-(1′,3′-dibenzyl-2′-ketoimidazolido)-1,2-trimethylene thiophanium *d*-camphor sulfonate], in induced hypotension during 52 major craniotomies, with three illustrative case reports. Arfonad proved to be a safe and adequate drug for this purpose. It was superior to the methonium compounds by virtue of its shorter action, which permitted greater control of blood pressure with satisfactory reduction of hemorrhage and intracranial pressure. Operative and postoperative hemorrhage and mortality were low. In none of the four postoperative deaths was there reason to believe that induced hypotension played any part in

the fatal outcome. The value of Arfonad in vascular lesions (aneurysm, angioma) is stressed.

MAXWELL

Bouchard, F., Laureus, P., and Allard, E.: Recording of Cardiovascular Pressures During Surgery. Arch. mal coeur. **46:** 905 (Oct.), 1953.

The authors desribe a new electronic manometer devised for obtaining intracardiac and intravascular pressures during surgery. The high frequency response of the instrument permits the puncturing of the chambers or big vessels with very fine needles without damping the curves. The entire manometric unit can be sterilized and placed into the field of operation. Except for occasional occurrence of premature beats, the punctures were well tolerated without development of subsequent hematomatas. The value of the methods lies in the direct confirmation at surgery of pulmonic or aortic stenosis, or of mitral insufficiency of dynamic importance. Alterations of cardiodynamics effected by valvotomy or comissurotomy can be evaluated immediately during the surgical procedure.

PICK

Baker, G. S.: Treatment of Multiple Aneurysms of the Internal Carotid Artery. Proc. Staff Meet., Mayo Clinic **28:** 668 (Nov.), 1953.

Multiple aneurysms of the carotid artery on the same side (one intracranial and the other in the carotid canal) are relatively rare. However, they offer an excellent outlook for a successful surgical approach, provided the two lesions can be trapped by ligation of the internal carotid artery in the neck, and ligation of the intracranial portion of the artery beyond the aneurysmal sac, without sacrifice of the arterial blood supply to the respective cerebral cortex. Careful determinations of the collateral circulation about the circle of Willis should be made before ligation. Cervical compression of the internal carotid artery (Matas test), and the demonstration of cross-filling of the vessels supplying the contralateral cortex through the anterior and posterior communicating arteries, can be determined at time of arteriography. When the results of preliminary studies are favorable for a surgical approach to the problem of aneurysm, the results of these procedures are invariably good. Such a case is demonstrated in the report, in which ophthalmic involvement produced a definite indication for treatment.

The prognosis for a complete cure seems excellent in this case. At the date of this report, more than two and one-half years since the operation, the patient was able to carry on as a normal person, and was free of any signs of the intracranial aneurysms.

SIMON

THROMBOEMBOLIC PHENOMENA

Fruhling, L., and Marcoux, F.: Paradoxical Emboli. Arch. mal. coeur **46:** 1013 (Nov.), 1953.

Six case histories are presented of paradoxic embolization proven by autopsy. Only such cases were included in the study in which the embolus was caught "in flagrante," i.e. wedged into an open foramen ovale or a ductus arteriosus. In all cases the crossing over of the clot from the venous into the systemic circulation occurred in the course of repeated embolization. Usually it is preceded by a massive pulmonary embolus creating pressure elevation in the right heart and thus conditions favorable for transfer of a thrombus from right to left. Although paradoxic embolization is compatible with survival of the patient, such an outcome is extremely rare once clinical signs have developed. Only in one instance among the six described cases did a paradoxic embolus to the brain occur several days before a fatal second embolization of the lungs.

PICK

VASCULAR DISEASE

Calenda, D. G., and Uricchio, J. F.: Gastrointestinal Hemorrhage due to Rupture of Aortic Aneurysm into the Esophagus. J.A.M.A. **153:** 548 (Oct. 10), 1953.

The authors present a case of spontaneous perforation of a syphilitic aneurysm of the descending aorta into the esophagus with hematemesis and melena. This case illustrates that the diagnosis of aorticoesophageal fistula should be considered in a patient with gastrointestinal hemorrhage when an aneurysm of the thoracic aorta is also present.

KITCHELL

Love, J. G.: Cellophane Wrapping of Abdominal Aortic Aneurysm. Proc. Staff Meet., Mayo Clin. **28:** 587 (Oct.), 1953.

There have not been many reports of successful direct surgical attack on aneurysms of the abdominal aorta. At times, the pain of this condition may be so severe as to be intolerable, and then the neurosurgeon may be confronted with the problem. A band of cellophane was passed around the aorta proximal to the aneurysmal sac and drawn tight. This band was sutured anterior to the aorta with the possibility in mind that the cellophane would produce slow fibrosis and occlusion of the aorta proximal to the aneurysm. A lumbar sympathectomy was attempted but could not be done for technical reasons. There was considerable relief of previously intractable pain postoperatively and the patient began to resume a more normal life.

Although the aortic aneurysm in this case was not cured by the operation performed, the intervention spared the patient much suffering that he otherwise undoubtedly would have experienced. He survived nine and one half months after surgery and finally died of rupture of the aneurysm which had almost completely disappeared.

SIMON

Wylie, E. J., and McGuinness, J.: The Recognition and Treatment of Arteriosclerotic Stenosis of Major Arteries. Surg., Gynec. & Obst. **97:** 425 (Oct.), 1953.

Four categories of patients are included in this study: 12 patients in whom a segmental zone of arteriosclerotic narrowing was the sole demonstrable cause for the presenting of complaints of arterial insufficiency; six patients in whom asymptomatic arterial stenosis was an incidental arteriographic finding; six patients whose original stenotic lesion progressed to complete thrombosis; and three patients who were found to have a significant stenotic lesion apart from a separate zone of arterial thrombosis.

In all patients, the pathologic changes involved a portion of the major arterial tree between the upper abdominal aorta and the level of bifurcation of the popliteal arteries. Resection of the diseased intima was performed in 12 patients. The authors further described their modification of the technic of aortography. Resection of the diseased intima was successful in restoring a normal arterial lumen and relieving the symptoms of ischemia in ten patients. The authors postulate that arterial stenosis of sufficient degree to produce ischemic symptoms represents an almost complete arterial occlusion and is a frequent intermediary stage in the development of arterial thrombosis.

DENNISON

Gillingham, J.: Arteriovenous Malformations of the Head. Edinburgh M.J. **60:** 305 (July), 1953.

The author reported on 18 cases of arteriovenous malformations of the head, of which seven were treated by surgical excision or by ventriculocisternostomy. Of the latter number, five survived. X-ray films of the skull, ventriculography and carotid and vertebral angiography were considered valuable aids in the diagnosis of this condition. Only in a minority of cases were bruits heard through the intact skull. However, when the lesion presented on the surface of the scalp or when there were large arteriovenous communications within the intracranial malformation, this sign was present. The bruit was usually intermittent, being audible only when blood flow was maximal.

Patients with arteriovenous malformations are more commonly men, between the age of 20 and 30 years. Attacks of epilepsy are frequent and they may take the form of a jacksonian type. There may also be evidence of intraventricular or intracerebral hemorrhage or both. A few patients may complain of unilateral headaches suggestive of migraine.

The lesion is a congenital malformation of the primitive vascular plexus of the head, giving rise to a conglomeration of smaller or larger abnormal arteries and veins which communicate through arteriovenous fistulas. The malformation may implicate not only cerebral arteries and veins, but occasionally, also, the meningeal vessels of the dura. The lesions may be quite small or they may be enormous.

ABRAMSON

Sloper, J. C., and Storey, G.: Aneurysms of the Ascending Aorta Due to Medial Degeneration Associated with Arachnodactyly (Marfan's disease). J. Clin. Path. **6:** 299 (Nov.), 1953.

The first case described by the authors was that of a woman, 24 years old at death, who had typical skeletal and ocular changes of Marfan's syndrome. Progressive aneurysmal dilatation of the ascending aorta with aortic regurgitation began in her teens. Histologically the involved portion of the aorta showed marked disruption of the elastic lamellae.

The second case was that of a woman, 55 years old at death, who did not have eye abnormality, and although the digits were long the limbs were thought to be normally proportioned. Grossly and histologically the aneurysm of ascending aorta was quite identical to that in the first case. The authors suggest that "the nonspecific medial degeneration of senescence" may produce aneurysms indistinguishable from those of Marfan's syndrome. No investigation of the family, often helpful in the elucidation of these doubtful cases, is described.

MCKUSICK

Nielsen, J. M.: Management of Cerebral Vascular Accidents. Ann. Int. Med. **39:** 717 (Oct.), 1953.

Cerebral vascular accidents are usually thought of as thrombosis, hemorrhage and embolism. However, subarachnoid hemorrhage and subdural hematoma are also vascular accidents. Neoplasms come in for differential diagnosis in many cases. The author reports the employment of stellate ganglion block during the preliminary phase of thrombosis. This preliminary phase is manifested by parasthesias or mild weakness, or, perhaps by visual disturbances. In addition, the intravenous infusion of 500 mg. of procaine in 500 cc. of normal saline over a two hour period is also recommended.

The old concept of a massive hemorrhage from sudden blowing-out of the large vessels is not common. More often, hemorrhage is by diapedesis, and in a number of cases this may give focal neurologic signs as though the lesion were a neoplasm. This type is favorable for surgical drainage. If the lesion is left it becomes a foreign body and may easily cause epilepsy. The massive cerebral hemorrhage is so serious a condition, accompanied as it usually is by coma, that there is little to be done.

The hemiplegia due to subdural hematoma differs from that due to intracerebral hemorrhage or thrombosis by being spastic initially and remaining so. The author points out that the classic syndrome of subdural hematoma embodies a history of trauma and immediate loss of consciousness, but with apparent recovery; subsequently there occurs the development of headache, progressive stupor, ipsilaterally dilated and poorly reacted pupil, hemi-

plegia and signs of increased intracranial pressure. This classic picture may not always be encountered and indeed the intensity of the head trauma may actually be forgotten or be minimal.

Congenital aneurysms of the Circle of Willis tend to give symptoms before rupture and a different syndrome after leakage or frank rupture. The anomalies also called malformations, give symptoms which depend on the anatomic location, and no one syndrome can profitably be described. On the other hand, the common saccular aneurysms of the Circle of Willis tend to cause headaches diagnosed as migraine. For this reason, persistent, recurrent migraine syndromes which remain fairly fixed anatomically (i.e., headaches always in the same area or headache associated with extraocular palsy) should arouse suspicion of aneurysms. Angiography is then justifiable.

DENNISON

Ahlström, C. G., Liedholm, K., and Truedsson, E.: Respirato-Renal Type of Polyarteritis Nodosa. Acta med. scandinav. **144:** 323 (Fasc. 5), 1953.

Two cases of polyarteritis nodosa are described in which the major symptoms and anatomic changes were confined to the respiratory tract and kidneys. The first patient was a man aged 70 years who had fever, chills, pain in the chest, fatigue and dyspnea. Radiographic studies showed lesions in the lungs suggesting metastases. The patient died in uremia after an illness of two months. Postmortem examination disclosed numerous infarct-like necrotic foci in the lungs, necrotic islands in the spleen, and signs of nephritis. Vascular changes of the type seen in polyarteritis nodosa were present in the lungs, spleen and kidneys. The second patient was a woman, aged 41 years, who had a sinusitis initially followed by joint pain, fever, transient diabetes insipidus, corneal ulcers and scleritis. Crusting rhinitis, laryngitis, pulmonary parenchymal densities, pustular and necrotic papules of the skin were later manifestations. The patient died in uremia one year after the initial symptoms. Postmortem examination disclosed necrotic foci and vascular lesions with fibrinoid necrosis and perivascular, inflammatory, cellular infiltration in the neighborhood of the foci in the lungs and kidneys. These cases are compared with other similar ones previously reported, particularly those of Wegener, and it is suggested that they be classed as a special type of polyarteritis nodosa.

ROSENBAUM

Oliner, L., Taubenhaus, M., Shapera, T. M., and Leshin, N.: Nonsyphilitic Interstitial Keratitis and Bilateral Deafness (Cogan's Syndrome) Associated with Essential Polyangitis (Perarteritis Nodosa). A Review of the Syndrome with Consideration of a Possible Pathogenic Mechanism. New England J. Med. **248:** 1001 (June 11), 1953.

The writers report a case of nonsyphilitic interstitial keratitis with deafness occurring in a woman age 23 years who had had two episodes of oculo-aural symptoms, followed by the development of extensive vascular symptoms due to polyangitis with involvement of the gastrointestinal tract, skin, heart, pleura and sclera. The opinion is expressed that polyangiitis is the end result of a sequence of events including: (1) a nonspecific antigenic or injurious agent; (2) production of a specific abnormal globulin, associated with mechanical stress; or (3) sustained local hydrostatic pressure resulting in vascular lesions. Etiologic agents which are considered possible factors in this case include infection of the teeth and urinary tract due to hemolytic streptococci, cortisone which was used for the oculo-aural symptoms but may have disseminated the infection and endogenous steroids secreted during the second half of the menstrual cycle.

ROSENBAUM

Elkeles, A.: Peptic Ulcer in the Aged and Gastric Carcinoma in their Relationship to Arteriosclerosis. Am. J. Roentgenol. **70:** 797 (Nov.), 1953.

In a series of 116 cases with gastric ulcer there was associated calcification of the abdominal aorta on roentgenograms in 64 to 100 per cent, rising with each decade level. In patients with duodenal ulcer of the same age levels the percentage of aortic calcification was 21 to 70 per cent. In gastric carcinoma the incidence was from 0 to 14 per cent.

From this data the author concludes that the frequent association of aortic calcification with gastric and duodenal ulcers may be useful in differentiating small or large benign lesions from similar appearing lesions in gastric carcinoma, where the incidence of aortic calcification was much less frequently found.

SCHWEDEL

Weissman, J., and Tagnon, H. J.: Syndrome of Hemangioma and Thrombocytopenic Purpura in Infants. Arch. Int. Med. **92:** 523 (Oct.), 1953.

Two cases are reported which illustrate the association of thrombocytopenia with hypertrophic hemangioma in infants. It is probable that this association represents a real syndrome. Regression of the hemangioma coincided with the disappearance of thrombocytopenia. Splenectomy did not affect the thrombocytopenia in one case in which it was done.

BERNSTEIN

Ross, R. S., and McKusick, V. A.: Aortic Arch Syndromes. Arch. Int. Med. **92:** 701 (Nov.), 1953.

The classification and discussion presented here are based on a review of over 100 cases of aortic arch syndrome of which 35 are previously unreported. Syphilitic aortitis is undoubtedly the most common

cause of this syndrome. The presence of aneurysm is by no means essential. In fact, saccular aneurysm was present in less than half of the cases with great vessel obstruction due to syphilis of the aorta. In all cases of syphilitic origin, with and without aneurysm, intimal proliferation and cicatrization represent by far the most common mechanisms of obstruction. In only 3 of 44 cases, for instance, was antemortem thrombus (a phenomenon seen only in saccular aneurysm) responsible for the occlusion. Secondary atheromatosis of the syphilitic aorta is undoubtedly an important contributing factor in great vessel obstruction. Atheromatosis is surprisingly uncommon as a primary cause but may contribute in the traumatic and congenital cases, as it almost certainly does in those of syphilitic aortitis.

Attention is drawn to the unsolved and confused problem of arteritis of the larger vessels. In most cases of involvement of the aorta and its large arch branches, it is uncertain whether the process represents Buerger's disease, periarteritis nodosa, "giant cell arteritis," or some other disorder. The clinical manifestations result almost exclusively from the impediment to carotid artery blood flow (interference with vertebral blood flow by obstruction of the subclavian arteries is doubtless an additional factor of importance in some cases). Whereas cerebral, eye, ear, and face changes are outstanding features of the clinical picture in some cases, symptoms referable to the arms are conspicuous by their absence. Therapy can be directed at the etiologic factor, in the case of syphilis at least, and striking benefit has been observed in two patients. Surgical approaches to the treatment of all varieties of the aortic arch syndrome should be explored further.

BERNSTEIN

Walder, D. N.: The Local Clearance of Radioactive Sodium from Muscle in Normal Subjects and Those with Peripheral Vascular Disease. Clin. Sc. **12:** 153 (May), 1953.

The author compared the results of blood flow studies through muscle using the rate of local clearance of radioactive sodium with those obtained by means of the venous occlusion plethysmograph. The investigation was carried out in normal subjects and in patients with obliterative arterial vascular diseases.

It was the author's conclusion that the clearance rate of radioactive sodium injected into a normal muscle was not directly related to blood flow, but was related to the state of the capillary bed. However, marked differences were noted during exercise in the clearance of the material from the muscles of normal subjects compared with those suffering from intermittent claudication. Because of this, it was suggested that the test could be used in patients with occlusive arterial vascular disease for the evaluation of therapy, presumably affecting muscle circulation.

ABRAMSON

Sullivan, B. J., and Covino, B. G.: Peripheral Vascular Responses to Frostbite as Influenced by Alcohol. Am. J. Physiol. **175:** 61 (Oct.), 1953.

When 15 per cent alcohol was given by intrapentoneal injection it could either prevent or alleviate vasoconstriction due to frostbite. In either case the effect was only temporary but was more sustained if given as premedication. Blood sludge, a uniform gel-like mass embracing almost all formed elements, was seen in direct frostbite and alcohol therapy.

OPPENHEIMER

Pick, A., and Mininni, G.: The Mechanism of Sudden Death in Dissecting Aneurysm with Intracardiac Rupture. Brit. Heart J. **15:** 369 (Oct.), 1953.

The authors report an instance in a man 74 years old of a dissecting aneurysm of the aorta that ruptured and also produced hemorrhage in the region of the auricular ventricular node. The electrocardiogram that was recorded for 40 minutes after clinical death showed disturbances in conductivity involving successively the auricles, the A-V conduction and intraventricular conduction. Sinus slowing alternating with rapid phases of auricular activity were recorded as well as idiopathic ventricular activation. The first phase was regarded by the authors as due to the hemorrhage involving the A-V node.

The authors conclude that the ventricle is the last portion of the heart to function electrically.

SOLOFF

Sinclair, W., Jr.: Dissecting Aneurysm of the Middle Cerebral Artery Associated with Migraine Syndrome. Am. J. Path. **29:** 1083 (Nov.–Dec.), 1953.

The author reports on a 27 year old housewife who is unique in the medical literature for association of migraine with dissecting aneurysm. Dissecting aneurysm of a cerebral artery has been reported in only three instances. Unlike dissection of the aorta, the dissection was subintimal. Compression occlusion of the artery resulted in infarction of the brain.

MCKUSICK

OTHER SUBJECTS

Sharpey-Schafer, E. P.: The Mechanism of Syncope After Coughing. Brit. Med. J. **2:** 860 (Oct. 17), 1953.

Intrathoracic pressures of 300 mm. Hg were attained in some instances by continuous coughing. Consciousness was usually lost during the period of acute hypotension following cessation of coughing. The hypotension was clearly due to a fall in left ventricular output as a result of impeded venous

return to the heart. Intermittent coughing and continuous coughing produced different physiologic effects: peripheral resistance fell and forearm blood flow rose with intermittent coughing, whereas converse changes occurred with continuous coughing. The author presents clinical considerations and states that he believes syncope after coughing is a much more common phenomenon than indicated in the literature inasmuch as he was able to collect 27 cases.

McKusick

Freed, E. X., and Cruickshank, W. M.: The Relation of Cardiac Disease to Feelings of Fear. J. Pediat. **43:** 483 (Oct.), 1953.

Similarities and differences between a group of cardiac children, a mixed handicapped group, and a group of physically normal children in the area of fear and anxiety is presented by statistical analysis of responses to test sentences. A fear of their handicap significantly differentiated the cardiac group from their matched, physically normal controls. In the adjustments to parents and family and in evaluating their adjustment, however, the cardiac children were more similar to their control group than the total handicapped group was to its control group. The data did not indicate that the adjustment of the cardiac child was regressive or immature.

Maxwell

Stopak, J. H.: Effect of Ferritin on the Mortality of Mice Subjected to Tourniquet Shock. Am. J. Physiol. **175:** 99 (Oct.), 1953.

Mortality rates following tourniquet shock were not significantly influenced by 100 micrograms of Ferritin N/20 Gm. injected in mice. However, 1000 micrograms produced toxic phenomena. The relationship to shock is not clear.

Oppenheimer

Mattox, V. R., Mason, H. L., and Albert, A.: Isolation of a Sodium-Retaining Substance from Beef Adrenal Extract. Proc. Staff Meet., Mayo Clin. **28:** 569 (Oct.), 1953.

Chromoatographic procedures have been used to isolate from beef adrenal extract a crystalline substance with sodium-retaining properties which are qualitatively similar to but quantitatively much greater than those of desoxycorticosterone acetate (DOCA). This diacetate was hydrolyzed enzymatically to give the free substance which was about 100 times as active as DOCA in bio-assays. The hydrolytic procedure also produced another substance, considered to be a monoacetate, which was obtained in crystalline form and which was about 25 times as active as DOCA.

Assuming that the fundamental structure is similar to that of the adrenal hormones, the results of ultraviolet and infrared spectroscopic examination of these products and various chemical reactions suggest the tentative conclusion that the unacetylated sodium-retaining substance is an isomer of corticosterone.

Simon

Friedberg, C. K., Taymor, R. C., and Minor, J. B.: Spontaneous Antidiuresis during Water Diuresis: Renal Function and Electrolyte Excretion. J. Lab. & Clin. Med. **42:** 509 (Oct.), 1953.

The occurrence of a spontaneous antidiuresis in a water-loaded normal subject was associated with an extreme reduction in both glomerular filtration and in renal plasma flow, during the first 30 minutes of antidiuresis. Intense renal vasoconstriction is suggested as the mechanism. There was also an extreme reduction in excretion of sodium and chloride with little increase in concentrations; this was correlated with the fall in glomerular filtration rather than with the endogenous stimulation of antidiuretic hormone (ADH).

A second period of antidiuresis was followed by a 30-minute period of reestablished diuresis during which glomerular filtration and renal plasma flow rebounded to rates greater than twice normal. The electrolyte excretion similarly exceeded its initial values. These findings denoted a period of renal vasodilatation following the period of renal vasoconstriction. The urinary flow did not exceed the initial diuresis despite glomerular hyperfiltration; this was probably due to the higher percentage of tubular reabsorption of water than in the first 30-minute period.

Antidiuresis following pitressin lasted only two 15-minute periods. During the first 15-minute period there was a significant fall in glomerular filtration, renal plasma flow and excretion of electrolytes which was apparently due to renal vasoconstriction. The second 15-minute period of antidiuresis was unlike that which occurred spontaneously, in that it was independent of changes in glomerular filtration and renal plasma flow. These changes were normal as was sodium and chloride excretion. The higher percentage of tubular reabsorption of filtered water also suggested that the antidiuresis during this period was due to the antidiuretic factor present in the injected pitressin without concomitant alteration in blood flow. No such period was observed during the period of spontaneous antidiuresis.

The observation of spontaneous antidiuresis in association with renal vasoconstriction and reduction in electrolyte excretion as well as the subsequent renal hyperfunction suggests the importance of considering the possible occurrence of these effects when interpreting observations on diuresis, antidiuresis and on electrolyte excretion in man.

Mintz

Ledingham, J. M.: The Distribution of Water, Sodium and Potassium in Heart and Skeletal Muscle in Experimental Renal Hypertension in Rats. Clin. Sc. **12:** 337 (Nov.), 1953.

Renal hypertension was produced in rats by the

application of a clip to one renal artery. Total body and tissue extracellular fluid were measured by a method using inulin. The total body extracellular fluid volume was found to be higher in experimental renal hypertension than in control animals, but this difference disappeared as the duration of the hypertension increased. An increase in extracellular fluid volume is therefore not essential for the established state of renal hypertension.

Accompanying the rise in extracellular fluid volume, was an increase in extracellular fluid in heart and skeletal muscle, accounting for the observed increased sodium and decreased potassium in heart muscle. There was no evidence of alteration of intracellular concentration of potassium in heart or skeletal muscle in renal hypertension. Nor was there a significant change in the normal ratio of intracellular fluid to total solids in cardiac or skeletal muscle. This is considered as evidence against the presence of cellular overhydration in experimental renal hypertension.

ENSELBERG

Malmros, H., and Swahn, B.: Lipid Metabolism in Myxedema. Acta med. scandinav. **145:** 361 (No. 5), 1953.

The lipid metabolism of 13 patients with myxedema was studied. The serum cholesterol, total lipids and phospholipids were increased in all patients. Electrophoretic analysis of the serum lipids showed marked elevation of the β-fraction much as had been recorded by the same observers in familial hypercholesterolemia and in some cases of myocardial infarction. The abnormalities in lipid metabolism were readily controlled by treatment with synthetic *l*-thyroxin or other suitable thyroid preparations. Analyses of serum lipids such as these have been found often to be more satisfactory methods of measuring thyroid function than determination of the basal metabolic rate.

ROSENBAUM

Wade, O. L., Bishop, J. M., Cumming, G., and Donald, K. W.: A Method for the Rapid Estimation of the Percentage Oxygen Saturation and Oxygen Content of Blood. Brit. M. J. **2:** 902 (Oct. 24), 1953.

The differences and possible advantages of this seemingly very accurate spectrophotometric method are: (1) that the standard laboratory models of spectrophotometer can be used rather than the more expensive Beckman type; and (2) that a single tube is used, obviating the necessity for matched tubes of special optical glass.

MCKUSICK

Buckley, J. P., Edwards, L. D., and Hiestand, W. A.: Effect of Discontinuous Decompression on Blood Pressure in the Rat. Am. J. Physiol. **175:** 93 (Oct.), 1953.

This study seeks to evaluate the effect of decompression with adequate oxygen upon observations which are ordinarily attributed to anoxia at high altitudes. Rats became hypertensive when exposed to 30,000 feet for two hours per day for 10 weeks Although observed for eight weeks more the hypertension had no effect on the development of the hypertension or its persistence. The authors express the opinion that the results are due to physical pressure reduction since the red cell count did not change during the decompression and anoxia could be considered not to play a role. In the lungs the alveoli were larger with narrow walls. The uriniferous tubules of the kidney were somewhat dilated.

OPPENHEIMER

Julian, D. G.: Epiphrenic Oesophageal Diverticulum with Cardiac Pain. Lancet **6792:** 915 (Oct. 31), 1953.

A case of epiphrenic diverticulum of the esophagus is presented, in which the patient had chest pain brought on not only by bending forward, lying down, and swallowing solids, but also by exercise and relieved by rest. The electrocardiogram showed T-Wave inversion in leads I and V_4 which became upright on one occasion after evacuation of the diverticulum and again following resection of the diverticulum. It is postulated that coronary vasoconstriction probably resulted indirectly from distension of the diverticulum, possibly by means of a vagal reflex.

MAXWELL

Miller, H., Uricchio, J. F., and Phillips, R. W.: Acute Pericarditis Associated with Infectious Mononucleosis. New England J. Med. **249:** 136 (July 23), 1953.

Three cases of acute pericarditis occurring in two young men and one young woman with infectious mononucleosis are reported. In each case there was clinical, hematologic and serologic evidence of infectious mononucleosis at some time during the illness. Electrocardiographic changes of considerable extent, in both RS-T segments and T waves appeared in all cases. Considerations of the pathogenesis of the acute pericarditis include: (1) extension of the infection from the hilar lymph nodes into the pericardial sac; (2) a virus infection of the pericardium; and (3) a response of the pericardium as a shock organ to an offending allergen in a sensitive person.

ROSENBAUM

Moschcowitz, E.: Pathogenesis of Constrictive Pericardium. J.A.M.A. **153:** 194 (Sept. 19), 1953.

The pathogenesis of seven cases of constrictive pericardium which came to postmortem examination is discussed. Four of these cases had the classic clinical signs and symptoms of constrictive peri-

cardium. Three of them, however, lacked many of the signs and symptoms though they had many of the anatomic characters and unusually thick totally adherent pericardiums. These latter three cases are viewed by the author as potentially constrictive pericarditis, in other words as an earlier phase of the disease. Etiologically these cases are one of the late results of polyserositis whether from tuberculosis, rheumatic fever, or associated with an indeterminate endocarditis, possibly of the type described by Libman and Sacks. Only a postmortem examination is decisive in determining the precise cause.

KITCHELL

Fourman, P., and Robinson, J. R.: Diminished Urinary Excretion of Citrate During Deficiencies of Potassium in Man. Lancet **265**: 656 (Sept. 26), 1953.

Potassium deficiency was induced in two normal men by the ingestion of a cation-exchange resin and a low potassium diet. During the potassium deficiency state the urinary excretion of citrate was diminished as compared to the control conditions. The citrate excretion remained low and returned to control values only when the potassium deficiency had been completely corrected. There was no fall in plasma citrate levels associated with the low urinary citrate excretion. Urinary excretion of citrate was also found to be diminished in a woman with renal acidosis and potassium deficiency.

SAGALL

Hutcheson, J. M. Jr., Hejtmancik, M. R., and Herrman, G. R.: Changes in the Incidence and Types of Heart Disease. A Quarter-Century Follow-Up in a Southern Clinic and Hospital. Am. Heart J. **46**: 565 (Oct.), 1953.

This report deals with a statistical study made of organic heart disease in consecutive new clinic and hospital patients in a Southern medical center from September 1951, through February 1953. This series includes 1,000 patients and is compared with two previous reports by the authors. The incidence of organic heart disease is still greater in the Negro than in the White, but much less so than 25 years ago. The incidence of hypertensive heart disease is approximately the same as before, but that of arteriosclerotic heart disease has increased. There has been a tenfold increase in the diagnosis of congenital heart disease. Syphilitic heart disease has decreased and is infrequent; rheumatic heart disease has shown little change in frequency, but there has been a slight decrease in bacterial endocarditis. Hypertension is still more common in the Negro than in the White, while arteriosclerosis is less frequent. However, the peakage incidence of hypertension occurs a decade later in each race than in the previous studies. There has been a striking increase in the diagnosis of angina pectoris.

RINZLER

Mufson, I.: An Etiology of Scleroderma. Ann. Int. Med. **39**: 1219 (Dec.), 1953.

Evidence collated from a clinical and psychologic study of several patients supports the belief that scleroderma, like Raynaud's disease, is a manifestation and the result of a psychosomatic disturbance with a definite pattern. The patient's sense of security always depends upon a commensalistic type of existence. When, by force of circumstances, this is destroyed, the inflexible nature of his personality does not permit readjustment. The dread fear initiates a generalized spasm of the minute vessels and the evolution of cutaneous and visceral scleroderma. While this life situation is operative, the process persists and is cumulative in its self-destruction. If and when security is re-established, by chance or design, the process is reversed and the complicating thrombotic manifestations become amenable to vasodilating therapy. To attempt such therapy without first re-establishing security is to court failure and disappointment which, in turn, aggravate the disease. Though the problem is presented from the medical viewpoint, the cooperative help of the psychiatrist, the surgeon, the psychologist and the social worker was required to gain this insight, which frequently prevented the evolution of simple vasospasm to scleroderma.

WENDKOS

Frank, H. A.: Present-Day Concepts of Shock. New England J. Med. **249**: 445 (Sept. 10), 486 (Sept. 17), 1953.

The author has extensively reviewed the recent literature pertaining to shock. So far as pathogenesis is concerned, it is pointed out that there is clear correlation between the severity of shock and the degree of reduction in the circulating blood volume. Shock of moderate or severe degree appears when the blood volume is reduced by about 35 to 40 per cent of its normal value. The blood is lost from and into the area of injury. "Wound shock" is due to whole-blood loss complicated by the other effects of the wound. Neurogenic and toxic factors are much less important in the production of shock except when there is overt sepsis.

Recent observations have reaffirmed the usefulness of the standard clinical observations in shock. The blood-volume deficiency is 30 per cent or more when the arterial pressure has dropped below 100, as a result of blood loss. When the hematocrit is high, elevation in peripheral resistance due to increased blood viscosity tends to sustain the arterial pressure as the cardiac output fails; the arterial pressure levels may lead to a false estimation of the circulatory state under these circumstances. It is mentioned that cerebral thrombosis and coronary thrombosis are not uncommon in older patients who have suffered shock, the latter when coronary blood flow falls below critical levels for myocardial viability or due to thrombosis precipitated within diseased coronary vessels. Liver function may be seriously

impaired in shock because a large part of the blood flow and oxygen supply of this organ is venous. Renal blood flow is sharply reduced in shock and urine formation ceases when the arterial pressure falls below 60 to 80. The major pathogenic factors in the production of lower nephron nephrosis in injured men are believed to be renal ischemia due to shock and hemoglobinemia or myoglobinemia. The adrenal cortex response to shock is found in the metabolic response, the fall in circulating eosinophils, the increased excretion of ketosteroids and corticoids in the urine, and histologic changes seen at death. Congestion and ulceration of the gastrointestinal mucosa also develop in shock.

In the therapy of wound shock, surgical treatment of the wound is a major feature. Replacement of the blood volume with whole blood is imperative. A urine formation of 1 cc. of urine per minute is considered an index of adequate peripheral blood flow. Resumption of urine flow is prompt if due to dehydration. Excessive fluid therapy should be avoided if anuria or oliguria persist. Plasma is useful for restoring smaller blood-volume deficits, and it has the advantage that it may be stored for long periods but the disadvantage of the risk of viral hepatitis. The author cites the view of Beecher that ether is the safest anesthetic agent for severely injured men. There is said to be no convincing evidence that adrenocortical therapy enhances resistance to shock. Intra-arterial transfusions are believed to have their chief usefulness as a resuscitative measure when the heart has stopped. Severe infection may produce shock in the absence of trauma, and shock of this type is not corrected by plasma or whole-blood replacement unless the sepsis is also controlled.

About 10 to 15 per cent of patients with myocardial infarction are said to manifest signs of shock, and the mortality rate in these patients is 80 to 90 per cent. This shock is associated with a nearly 50 per cent reduction in cardiac output and stroke volume, and a peripheral resistance and circulation time which is nearly doubled. Blood volume and central venous pressure are not reduced. The dilemma presented here is that therapy which will improve peripheral and coronary blood flow will also increase the work load of the heart.

ROSENBAUM

Rose, J. C., Gilford, S. R., Broida, H. P., Soler, A., Partenope, E. A., and Fries, E. D.: Clinical and Investigative Application of a New Instrument for Continuous Recording of Blood Pressure and Heart Rate. New England J. Med. **24**: 615 (Oct. 8), 1953.

A physiologic monitor is described which makes possible a continuous recording of the blood pressure, heart rate, respiratory rate and minute respiratory volume. The blood pressure is automatically measured by a modification of standard auscultatory methods. A microphone pickup is placed over the brachial artery and covered by a standard inflatable arm cuff which is slowly inflated by an air compressor. The first pulse beat detected by the microphone activates a diastolic blood-pressure indicator. Inflation of the cuff continues until the pressure reaches a point 10 mm. Hg above the last recorded pulse beat. The cuff pressure is then released automatically until the first pulse beat detected activates the systolic blood-pressure indicator. Pressure in the cuff is then released to 0. The pressures are recorded on a Speedomax chart which may be located at any distance from the patient. The measurement cycle is repeated every three minutes. An electric and a mechanical safety valve each prevent excessive inflation of the cuff. The heart rate is recorded continuously by an electronic circuit which measures the interval between R waves, using standard electrocardiographic leads and recording on the Speedomax chart.

Although designed primarily for use in the operating room, this monitor has been useful on the medical wards to study the effect of drugs as well as in routine medical and investigative efforts.

ROSENBAUM

Renzi, A. A., and Gaunt, R.: Apresoline (1-hydrazinophthalazine) in the Experimental "Eclampsia-Like" Syndrome and Related Aspects of Water Metabolism. Am. J. Physiol. **175**: 313 (Nov.), 1953.

Unilateral nephrectomized rats were given a high salt diet and desoxycorticosterone acetate (DCA). When renin was added edema, kidney damage and death resulted. These findings bear some resemblance to toxemia of pregnancy. If 1-hydrazinophthalazine (Apresoline) were given with the renin, the rats did not die and most of the aspects of the syndrome were prevented. Under the condition of these experiments, both renin and DCA (in presence of Apresoline) caused such diuresis that daily urine volumes exceeded the body weight. Apresoline alone (in doses used here) decreased salt and water excretion in normal rats. Rats treated with Apresoline were more susceptible to water intoxication. If Apresoline were used in normal rats in doses which did not produce hypotension, there was no effect on water and salt excretion.

OPPENHEIMER

Maloney, J. V., Jr., Smythe, C. McC., Gilmore, J. P., and Handford, S. W.: Intra-Arterial and Intravenous Transfusion; a Controlled Study of Their Effectiveness in the Treatment of Experimental Hemorrhagic Shock. Surg., Gynec. & Obst. **97**: 529 (Nov.), 1953.

Hemorrhage was accomplished in 64 days by permitting the animals to bleed freely from an indwelling arterial needle into a suspended reservoir. The period of hypotension varied from 30 minutes to four hours. The following significant observations were made: (1) The hydraulic effect of intra-arterial

transfusion, in elevating arterial blood pressure is insignificant at rates of transfusion which are presently employed clinically. (2) Recovery of arterial pressure is a function, not of the route, but of the rate of transfusion. (3) Intra-arterial and intravenous transfusions are equally effective in restoring the low cardiac output typical of hemorrhagic shock. (4) The rapidity with which intra-arterially and intravenously transfused blood mix with the general circulation was determined by a method in which the plasma fraction of the transfused blood was tagged. No evidence of pooling of the infused blood was found with either intra-arterial or intravenous transfusion. (5) Central venous pressure was found to fall during hemorrhage and to rise to normal or slightly above during reinfusion of previously shed blood. (6) Simultaneous, paired, survival experiments in 26 animals failed to show a significant difference in survival rate between intra-arterial and intravenous transfusion. (7) Direct perfusion of the coronary arteries by arterially infused blood was demonstrated by radiographic technic to occur only when the output of the left ventricle has become negligible or nonexistent. (8) In resuscitation from asystole, intra-arterial transfusion has some theoretic advantages over intravenous transfusion. (9) Direct perfusion of the cerebral vessels with unsaturated blood given intra-arterially was shown by direct oximetry to reduce both cerebral-arterial and cerebral-venous oxygen saturation. (10) No evidence could be found that rapid intra-arterial transfusion is any more or less effective than rapid intravenous transfusion of blood.

DENNISON

Ruben, J. E., and Mayer, R. A.: Is Stellate Ganglion Block of Value in Stroke? J. A. M. A. **153:** 1002 (Nov. 14), 1953.

A report is made on 58 patients with apoplexy who were treated to maximum benefit with stellate ganglion block in addition to usual routine management. Forty-three had conditions of less than one month duration and were therefore considered acute. The other 15 were first seen more than one month after the onset and were classified as chronic. Of the acute cases, 26 were improved, eight were not improved, and nine died. Of the chronic cases four were improved, and 11 were not improved. More than 60 per cent of the persons showed some improvement immediately after the appearance of Horner's syndrome. In almost 70 per cent of those showing improvement, the benefits were striking. Increase in muscle power and control has been observed to follow stellate ganglion block within minutes after the injection is given. The authors feel that on the basis of their experience and results, stellate ganglion block in experienced hands is innocuous and that, until some more definitive therapy is devised, patients suffering from stroke due to embolism, thrombosis, or spasm should not be denied the possible benefits of this therapeutic measure.

KITCHELL

Mendelson, S. N., and Iglauer, A.: Acute Abdominal Condition Due to Bishydroxycoumarin (Dicumarol) Poisoning. Arch. Int. Med. **92:** 760 (Nov.), 1953.

Two cases are reported of bishydroxycoumarin (Dicumarol) poisoning, in which the predominant early clinical findings were those of an acute abdominal condition. In one instance either the clinician failed to impress the patient with the importance of returning at regular intervals for prothrombin determinations or else the patient's low mentality should have warned against such reliance being placed upon her. In cases of suspected hemoperitoneum due to bishydroxycoumarin intoxication, immediate prothrombin levels should, of course, be ascertained. In addition, cul-de-sac aspiration offers a simple method of corroborating the diagnosis.

BERNSTEIN

Hobson, W., Jordan, A., and Roseman, C.: Serum-Cholesterol Levels in Elderly People Living at Home. Lancet **6793:** 961 (Nov. 7), 1953.

The mean serum-cholesterol levels in elderly men and women living at home were significantly higher than in control groups of younger prople. For both the young and the old, the mean serum-cholesterol levels in the women were significantly higher than in the men. There was a significant correlation between the dietary intake of fat and the serum-cholesterol level in women but not in men. Lifelong teetotalers had a higher level than had heavy drinkers. No relation could be established between, on the one hand, the serum-cholesterol level and, on the other hand, intermittent claudication, angina, cerebral thrombosis, aortic calcification, depressed crossing of the retinal blood vessels, arcus senilis, senile atrophy of the retina, senile cataract, or the height of the blood pressure.

MAXWELL

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Telephone Gramercy 7–9170

ASSOCIATION FELLOWSHIPS AND GRANTS

Applications for Research Fellowships and Established Investigatorships for the 1955–56 fiscal year *must be received on or before Sept. 15, 1954.* Applications for Research Grants-in-Aid must be received on or before Dec. 1, 1954. Information and application forms may be obtained from the Association's Medical Director.

SECOND WORLD CONGRESS OF CARDIOLOGY AND 27TH SCIENTIFIC SESSIONS OF AMERICAN HEART ASSOCIATION WASHINGTON, D.C., SEPTEMBER 12–17

Schedule of Events:

Saturday, Sept. 11, 5:00 to 10:00 p.m.: Registration, Mayflower Hotel

Sunday, Sept. 12:

9:00 a.m. to 10:00 p.m.: Registration, Mayflower Hotel

10:30 a.m.: Opening Ceremonies at Constitution Hall

8:30 p.m.: Reception for Congress Members, Pan American Building

Monday, Sept. 13 through Friday, Sept. 17: Scientific Sessions at National Guard Armory. (See program on page 476.)

Monday, Sept. 13: 8:30 to 10:30 p.m.: Visit to National Gallery of Art, for Congress Members only.

Tuesday, Sept. 14: 8:00 p.m.: Formal banquet for Congress Members, to be held simultaneously at the Mayflower and Statler Hotels.

Wednesday, Sept. 15, 2:30 to 5:30 p.m.: Medical sightseeing tours.

Thursday, Sept. 16: 8:30 p.m.: National Symphony Orchestra Concert

Friday, Sept. 17: 2:30 to 5:30 p.m.: Medical sightseeing tours.

A series of post-Congressional tours will include important University centers and cardiac clinics in the U. S. and Canada. Because it is essential to make travel arrangements in advance, all those planning to participate are urged to write for a descriptive booklet containing a form on which they may specify their choice of tours. *These forms should be filled out and returned at the earliest possible date.* The booklet may be obtained from L. W. Gorham, M.D., Secretary-General of the Congress, c/o American Heart Association, 44 East 23rd Street, New York 10.

SECTION ON CIRCULATION

In addition to presenting the George Brown Memorial Lecture of the American Heart Association Tuesday morning, September 14, at the Second World Congress of Cardiology, and a Tuesday afternoon Symposium, both in the Main Auditorium of the National Guard Armory, the Section on Circulation of the Association's Scientific Council has arranged several special events. The final revised program follows:

The Annual Dinner of the Central Advisory Committee of the Section will be held on Wednesday evening, September 15, at the Shoreham Hotel. A special Scientific Program will be held on Thursday afternoon, September 16, at 2:00 p.m. in Room 210S at the Armory.

BLAKESLEE AWARDS FOR SCIENTIFIC REPORTING

The 1954 Howard W. Blakeslee Awards of the American Heart Association will be presented at the banquet of the Second World Congress of Cardiology and the 27th Scientific Sessions of the Association in Washington, D. C., on Tuesday, September 14.

The Blakeslee Awards are presented annually to individuals whose creative efforts in any medium of mass communication are judged to have contributed most to public understanding of heart and circulatory diseases.

Second World Congress of Cardiology and 27th Annual Scientific Sessions of the American Heart Association, September 12–17, 1954, Washington, D.C.

Outline of Scientific Program——National Guard Armory

	Symposia, Round Table Discussions (Panels) and Lectures	Scientific Sessions			
	Main Auditorium—ROOM A	ROOM B	ROOM C	ROOM 12W	ROOM 27E
Mon. A.M.	Cardiovascular Epidemiology—Introductory Remarks Paul D. White Atherosclerosis Ancel Keys, *Chairman* Other Etiological Factors Paul D. White, *Chairman*	Electrocardiography (I)	Drugs and Therapy (I)	Physiology (I)	Occupational Cardiology and Rehabilitation
Mon. P.M.	Clinical Value of Instrumental Methods of Diagnosis in Congenital Heart Disease André Cournand, *Chairman* Indications for and Results of Operations in Congenital Heart Disease Helen B. Taussig and H. A. Snellen, *Chairmen*	Coronary Artery Disease	Drugs and Therapy (II)	Physiology (II)	Mitral Stenosis
Tues. A.M.	Rheumatic Fever Research—Experimental Studies on the Nature and Origin of Fibrinoid Lewis Thomas Diagnosis and Management of Rheumatic Fever and Rheumatic Heart Disease T. Duckett Jones and Maurice Campbell, *Chairmen* George Brown Memorial Lecture Alan C. Burton	Pulmonary Heart Disease	Cardiovascular Surgery (I)	Electrocardiography (II)	Arteriosclerosis and Cerebrovascular Disease
Tues. P.M.	Problems of Circulation George E. Burch and Grace M. Roth, *Chairmen* Prize Lecture of Argentine Society of Cardiology Manuel René Malinow Treatment of Hypertension Eduardo Braun-Menendez and Irvine H. Page, *Chairmen*	Rheumatic Fever and Rheumatic Heart Disease (I)	Cardiovascular Surgery (II)	Electrocardiography (III)	Ballistocardiography
Wed. A.M.	Blood Volume Gustav Nylin and Carl J. Wiggers, *Chairmen* Physiology of Contractile Protein in Heart Muscle Maurice B. Visscher, *Chairman*	Rheumatic Fever and Rheumatic Heart Disease (II)	Cardiopulmonary Dynamics	Vectorcardiography*	Congenital Heart Disease (I)
Thur. A.M.	Surgery of Congenital Heart Disease Alfred Blalock and Sir Russell C. Brock, *Chairmen* Surgery of Non-Congenital Heart Disease Robert E. Gross and Samuel A. Levine, *Chairmen*	Peripheral Vascular Disease†	Hypertension (I)	Heart Diseases of Uncommon Etiology (I)	Diagnostic Methods
Thur. P.M.	Memorial to Frank Norman Wilson Louis N. Katz Memorial to Willem Einthoven H. A. Snellen Electrocardiography Louis N. Katz, Charles E. Kossmann and George E. Burch, *Chairmen* Ballistocardiography Isaac Starr, *Chairman*	Hypertension (II)	Congenital Heart Disease (II)	Heart Diseases of Uncommon Etiology (II)	Phonocardiography and Auscultation
Fri. A.M.	Coronary Heart Disease Howard B. Sprague and Ramón Aixalá, *Chairmen* Charles Laubry Lecture Sir John Parkinson Closing Remarks Charles Laubry and Paul D. White	Subacute Bacterial Endocarditis	Pathology	Diagnostic and Therapeutic Instruments	X-Ray and Angiocardiography

* Special Symposium on Vectorcardiography—THURSDAY A.M., ROOM D, George E. Burch, *Chairman*

† Special Scientific Program—Section on Circulation—THURSDAY P.M., ROOM 210S, George E. Burch, A. Wilbur Duryee and Grace M. Roth, *Chairmen*

H. M. Marvin, M.D., Chairman of the Awards Committee, has announced the winners as follows:

Cathy Covert, medical writer, and Arthur Cornelius, chief photographer of the *Syracuse Herald-Journal*, for their series of ten articles on the heart diseases, appearing in the *Syracuse Herald-Journal*, December, 1953.

Clive Howard of Ridgewood, New Jersey, for his article, "Can Heart Disease Wreck Your Marriage?", published in the February, 1953 issue of the *Woman's Home Companion*.

"American Inventory," for "The Mechanical Heart," a documentary television program, telecast on NBC-TV, originating from Harper Hospital, Detroit, on February 15, 1953. The program was produced by William Hodapp with the assistance of Robert Wald, Laurence Schwab, Jr., and the staff of WWJ-TV, Detroit, with the cooperation of the General Motors Corporation and the Michigan Heart Association.

William A. Brams, M.D., of Chicago, Illinois, for his volume, "Managing Your Coronary," published by J. B. Lippincott Company of Philadelphia.

The winners will receive an honorarium of $500 each. Funds for the Blakeslee Awards have been made available by the Eva and Irving Hexter Foundation of Cleveland, the Robert Z. Greene Foundation of New York, and Frank N. Isbey of Detroit, a member of the American Heart Association's Board of Directors.

COUNCIL FOR HIGH BLOOD PRESSURE RESEARCH

The Annual Meeting of the Council for High Blood Pressure Research of the American Heart Association will be held in Cleveland on Friday and Saturday, October 22 and 23, at the Hotel Cleveland. The scientific program will open with a Friday morning session on "Nerve Transmission and Related Problems." Participants will include Amedeo Marrazzi, M.D., Army Medical Center, Md., and Steven W. Kuffler, M.D., Baltimore.

A program for lay members on Friday afternoon will feature a discussion on "Problems of Retirement" to be chaired by Irving S. Wright, M.D., New York. Participants will include Louis Karnosh, M.D., A. Carlton Ernstene, M.D., Edward Kline, M.D., Frank Joseph, and John Sherwin, all of Cleveland.

The scientific program on Saturday will be devoted to the subject of "Muscle Metabolism and Related Problems." Speakers at the morning session will include Wilfried F. H. M. Mommaerts, M.D., Cleveland, and Albert Szent-Györgyi, Woods Hole, Mass. Participants in the afternoon panel discussion will include Albert Szent-Györgyi, M.D., Wilfried F. H. M. Mommaerts, M.D., and Victor Lorber, M.D., Minneapolis.

The guest speaker at the Council's Annual Dinner on Friday evening will be Percival Bailey, M.D., Professor of Neurology and Neurosurgery, University of Illinois College of Medicine, Chicago.

COUNCIL ON RHEUMATIC FEVER AND CONGENITAL HEART DISEASE

J. G. Fred Hiss, M.D., Syracuse, N. Y., has been re-elected Chairman of the Council on Rheumatic Fever and Congenital Heart Disease. Katharine D. Brownell, M.D., New York, has been re-elected Vice-Chairman. New members elected to the Executive Committee of the Council were Edwin L. Harmon, M.D., Valhalla, N. Y., and John D. Keith, M.D., Toronto.

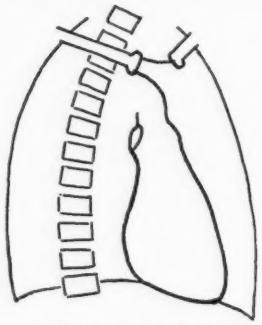
SUBSPECIALTY BOARD

Howard Wakefield, M.D., Chicago, has been named Chairman of the Subspecialty Board on Cardiovascular Disease of the Scientific Council of the Association to serve for two years. The Board examines candidates for certification as cardiologists by the American Board of Internal Medicine and advises the American Medical Association in the certification of hospitals for residency in this specialty.

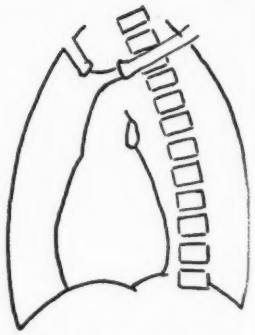
ANATOMIC CARDIAC STAMPS

Sets of anatomic cardiac rubber stamps are now available at cost to interested physicians to assist them in keeping records of heart patients. The rubber stamps were devised from diagrams in the book "Congenital Malforma-

Anterior-Posterior



Right Anterior Oblique



Left Anterior Oblique

tions of the Heart," by Helen Taussig, M.D., published by the Harvard University Press for the Commonwealth Fund.

Actual size imprints pictured above show outlines of the heart and chest which enable physicians to record fluoroscopic findings of disease conditions or abnormal changes in the heart shadow. They are available in three categories. 1. *Infant:* small size, 1½ x 1¼ inches; large size, 2 x 1¾ inches. 2. *Child:* small size, 1½ x 1¼ inches; large size, 1¾ x 1¾ inches. 3. *Adult:* one size only, 2 x 1¾ inches. Three views are available in each size: anterior-posterior, left anterior oblique and right anterior oblique.

The stamps are distributed nationally by the Stamford Heart Association, 190 W. Broad Street, Stamford, Connecticut, at the cost price of $3.00 for each category (three stamps), postpaid.

FILM ON ATHEROSCLEROSIS

A 16 mm. sound film, "Arteriosclerosis," has been made available by the American Heart Association to stimulate broader understanding of atherosclerosis. The film is a valuable educational and teaching aid intended for the general public, students, clinic and hospital patients, nurses and other professional personnel. It gives the layman a graphic explanation of what atherosclerosis is, underscoring the need for continued and intensified research on its cause and prevention, and for improved methods of treatment. The film was produced and directed by Sol S. Feuerman for the Association.

Rental charges for the film, which runs 13½ minutes, are $2.50 for three days plus shipping charges. The film may also be purchased at a cost of $60.00. Orders should be directed to the American Heart Association Film Library, 13 East 37 St., New York 16.

COURSE IN PRACTICAL ELECTROCARDIOLOGY

A course in practical electrocardiology will be presented from Dec. 6–10, 1954, under the auspices of the University of Texas Postgraduate School of Medicine, Baylor University College of Medicine and the Houston Heart Association. The guest lecturer will be Dr. Demetrio Sodi-Pallares, Chief of the Department of Electrocardiology of the National Institute of Cardiology of Mexico City. The course is primarily designed to acquaint general practitioners as well as internists with practical aspects of electrocardiology, with emphasis upon those tracings commonly encountered in practice. Further inquiry and advance registration may be made by writing the University of Texas Postgraduate School of Medicine, Houston, Tex.

INSTITUTE ON RHEUMATIC FEVER

The La Rabida Sanitarium, Chicago, will conduct an annual institute on rheumatic fever from Oct. 11–15, 1954. The institute will be conducted for four days by members of the hospital staff, together with participants selected from the medical schools in Chicago with which the hospital is affiliated, and by several invited guests.

The institute will be directed primarily to the general practitioner or family physician and to nurses, medical social workers, occupational therapists, dentists, and others with a similar interest in rheumatic fever and rheumatic heart disease. The fifth day of the institute, October 15, will be devoted to a scientific program concluding with the Robert A. Black lecture on rheumatic fever.

Further information may be obtained by writing the Institute, La Rabida Sanitarium, East 65 Street and South Shore Drive, Chicago 49, Ill.

ADDITIONAL RESEARCH AWARDS

In addition to the research awards for studies during the 1954–55 fiscal year announced in the July issue, the American Heart Association has approved the following new Grants-in-Aid, made possible by additional funds.

This brings to a total of 178 the number of research awards allotted this year as part of the joint research support program of the American Heart Association and its affiliates. A total of $996,105.71 has been approved for this program.

The latest awards were made as follows:

Grants-in-Aid

Yale University School of Medicine, New Haven, for the study of the response of arterial grafts to acute injury, by *William W. L. Glenn.* July 1, 1954–June 30, 1955. $5,250.00.

University of California, Berkeley, for the tracer studies of the intermediate metabolism of amino acids and related compounds of significance for hypertension and arteriosclerosis, by *David M. Greenberg.* July 1, 1954–June 30, 1955. $5,250.00.

University of Louisville, Louisville, for the studies on the venous system in dogs and man with special reference to the "collapsibility" of veins, and how this affects the pressure and flow through the venous system, by *Joseph Paynter Holt.* July 1, 1954–June 30, 1955. $5,250.00.

St. Luke's Hospital, New York, for the study of renal hemodynamics, albuminuria, and electrolyte excretion, by *John H. Keating.* July 1, 1954–June 30, 1955. $5,250.00.

Mount Sinai Hospital, Miami Beach, for the study of the histopathology of the conduction system in congenital heart disease, by *Maurice Lev.* July 1, 1954–June 30, 1955. $5,250.00.

Stritch School of Medicine, Chicago, for studies on electrolyte metabolism in the isolated mammalian heart, by *Akira Omachi.* July 1, 1954–June 30, 1955. $3,150.00.

Massachusetts General Hospital, Boston, for the study of the grafting of valve-containing veins into veins, by *Robert S. Shaw.* July 1, 1954–June 30, 1955. $3,675.00.

Southwestern Medical School of the University of Texas, Dallas, for the study of the use of ion exchange resins for quantitative analysis of biological material, by *John C. Vanatta.* Sept. 1, 1954–Aug. 31, 1955. $4,410.00.

Northwestern University Medical School, Chicago, for the study of the cytochemical changes that take place in the myocardium during injury, with special reference to ischemia and hypertrophy, by *William B. Wartman.* July 1, 1954–June 30, 1955. $5,250.00.

MEDICAL RESEARCH FELLOWSHIPS

The Division of Medical Sciences of the National Academy of Sciences-National Research Council is accepting applications for postdoctoral research fellowships for 1955–56. These awards are designed to offer research experience for promising individuals who look forward to investigative careers. Ordinarily fellowships are not granted to persons over thirty-five years of age.

The following awards are available: fellowships in cancer research, British-American exchange fellowships in cancer research, fellowships in the medical sciences, tuberculosis and radiological research. Applications for 1955–56 must be postmarked on or before Dec. 10, 1954. Fellowships are awarded in the early Spring. Complete details and application blanks may be obtained from the Fellowship Office, National Academy of Sciences-National Research Council, 2101 Constitution Avenue, N.W., Washington 25, D. C.

LIFE INSURANCE RESEARCH FUND FELLOWSHIPS AND GRANTS

Applications for awards available July 1, 1955, will be received by the Life Insurance Medical Research Fund as follows: (1) Postdoctoral research fellowships, until Oct. 29, 1954. Preference is given to those who wish to work on cardiovascular function and disease or related fundamental problems. Minimum stipend $3,500, with allowances for dependents and necessary travel. (2) Grants to institutions

in aid of research on cardiovascular problems, until Nov. 15, 1954. Support is available for physiologic, biochemical, and other basic work broadly related to cardiovascular problems as well as for clinical research in this field. Further information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 345 East 46th Street, New York 17, N. Y.

POSTGRADUATE SYMPOSIUM

The San Francisco Heart Association will present its Annual Postgraduate Symposium on Heart Disease Oct. 6, 7 and 8, 1954, in Larkin Hall of the Civic Auditorium.

Guest speakers will be Sir Russell C. Brock, London; Drs. Viking Olov Björk, Stockholm; Pedro Cossio, Buenos Aires; Horace Smirk, New Zealand.

Further information may be obtained from the San Francisco Heart Association, 604 Mission Street, San Francisco 5, Calif.

MEETINGS CALENDAR

Sept. 26–Oct. 2: World Medical Association; Rome, Italy; Louis H. Bauer, Secretary, 345 East 46th Street, New York 17.

Oct. 1954: Society of Clinical Surgery; Denver, Colo.; Champ Lyons, Secretary, 620 S. 20th Street, Birmingham 5, Ala.

Oct. 4–8: International Congress on Diseases of the Chest; Barcelona, Spain; Murray Kornfeld, Executive Secretary, 112 East Chestnut Street, Chicago 11, Ill.

Oct. 11–15: American Public Health Association; Buffalo, N. Y.; R. M. Atwater, Secretary, 1790 Broadway, New York 19.

Oct. 17–20: Association of American Medical Colleges; French Lick, Ind.; Dean F. Smiley, Secretary, 185 North Wabash Avenue, Chicago, Ill.

Oct. 22–23: Annual Meeting and Scientific Program, Council for High Blood Pressure Research, American Heart Association, Cleveland; Irving S. Wright, M.D., Chairman, Program Committee, % American Heart Association, 44 East 23rd Street, New York 10.

Oct. 25–30: College of American Pathologists, Washington, D. C., Arthur H. Dearing, Secretary, 203 North Wabash Avenue, Chicago, Ill.

Oct. 26–29: American Dietetic Association, Annual Meeting; Philadelphia; Mrs. Thelma Pollen, Public Relations Director, 620 North Michigan Ave., Chicago 11, Ill.

Oct. 31–Nov. 1: American Society for the Study of Arteriosclerosis, Annual Meeting; Sheraton Hotel, Chicago; Arthur C. Corcoran, M.D., Program Chairman, Cleveland Clinic, Cleveland, Ohio.

Nov. 3–5: National Society for Crippled Children and Adults, Annual Convention; Hotel Statler, Boston; Lawrence J. Linck, Executive Director, 11 South La Salle Street, Chicago 3, Ill.

Nov. 4–6: National Committee on Aging; New York, N. Y.; Mrs. Geneva Mathiasen, Secretary, National Social Welfare Assembly, 345 East 46th St., New York 17.

Nov. 29–Dec. 2: American Medical Association, Clinical Meeting; Miami; George F. Lull, M.D., Secretary, 535 North Dearborn St., Chicago 10, Ill.

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Circulation

SEPTEMBER 1954
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